Food and Drug Administration (FDA)

Center for Biologics Evaluation and Research (CBER)

Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting

Zoom Video Conference

January 26, 2023

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

Participants

Acting Chair	Stanley Perlman, M.D., Ph.D.	Professor, University of Iowa	Iowa City, IA
Members	Adam C. Berger, Ph.D.	Director, Clinical and Healthcare Research Policy, NIH	Bethesda, MD
	Hank Bernstein, D.O., MHCM, FAAP	Professor, Zucker School of Medicine	New Hyde Park, NY
	Archana Chatterjee, M.D., Ph.D.	Dean, Chicago Medical School	North Chicago, IL
	Amanda Cohn, M.D.	Chief Medical Officer, National Center for Immunizations and Respiratory Diseases, CDC	Atlanta, GA
	Hayley Gans, M.D.	Professor, Stanford University	Stanford, CA
	David Kim, M.D., M.S., M.H.A.	Director, Division of Vaccines, HHS	Washington, DC
	Paul Offit, M.D.	Professor, University of Pennsylvania School of Medicine	Philadelphia, PA
	Steven Pergam, M.D.	Professor, Fred Hutchinson Cancer Center	Seattle, WA
	Eric Rubin, M.D., Ph.D.	Professor, Harvard & Brigham and Women's Hospital	Boston, MA
Temporary Voting Members	Bruce Gellin, M.D., M.PH.	Senior Vice President, Rockefeller Foundation	Washington, DC
	James Hildreth, Sr., Ph.D., M.D.	President/CEO, Meharry Medical College	Nashville, TN
	Jeannette Yen Lee, Ph.D.	Professor, University of Arkansas for Medical Sciences	Little Rock, AR
	Ofer Levy, M.D., Ph.D.	Professor, Harvard Medical School	Cambridge, MA
	Pamela McInnes, DDS, MSc.	Retired Deputy Director, National Center for Advancing Translational Sciences, NIH	Bethesda, MD
	Cody Meissner, M.D.	Professor, Geisel School of Medicine; Dartmouth Hitchcock Medical Center	Lebanon, NH
	Michael Nelson, M.D., Ph.D.	Division Chief, University of Virginia	Charlottesville, VA
	Arthur (Art) Reingold, M.D.	Professor, University of California Berkeley	Berkeley, CA
	Mark Sawyer, M.D., FAAP	Professor, University of California San Diego	La Jolla, CA
	Melinda Wharton, M.D., M.PH.	Associate Director for Vaccine Policy, CDC	Atlanta, GA

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Consumer Representative	Randy Hawkins, M.D.	Faculty, Charles Drew University	Inglewood, CA
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	Filip Dubovsky, M.D.	Executive Vice President Chief Medical Officer, Novavax	Gaithersburg, MD
	Darin Edwards, Ph.D.	Senior Director of Immunology Infectious Disease Group, Moderna Inc.	Cambridge, MA
	Jefferson Jones, M.D., M.PH.	Medical Epidemiologist, National Center for Immunization and Respiratory Diseases, CDC	Bethesda, MD
	Nicola Klein, M.D., Ph.D.	Director, Kaiser Permanente Vaccine Study Center	Oakland, CA
	Ruth Link-Gelles, Ph.D., M.PH.	Epidemiologist, Division of Viral Diseases, NCIRD, CDC	Atlanta, GA
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FDA Participants/ Speakers	Peter W. Marks, M.D., Ph.D.	Director, CBER, FDA	Silver Spring, MD
	David Kaslow, M.D.	Director, Office of Vaccines Research and Review, CBER, FDA	Silver Spring, MD
	Jerry Weir, Ph.D.	Director, Division of Viral Products, OVRR, CBER, FDA	Silver Spring, MD

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	Kerri O'Neill		
	Russell Milko		
	Terry Jenkins		
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Contents

Call to Order and Welcome

Derek Bonner:Good morning, everyone. Today's date is January 26th, 2023. My name is Derek Bonner. I am a member of your AV support team for today's proceedings, and I'd formally like to welcome you to the 178th meeting of the Vaccines and Related Biological Products Advisory Committee. At this time, I'd like to hand our meeting over to our CBER Director, Dr. Peter Marks. Dr. Marks.

Dr. Marks: Thanks very much and good day wherever you may be tuning in from. I want to thank you very much for joining us for this 178th meeting of the Vaccines and Related Biological Products Advisory Committee meeting. I just want to let you know as we get started that due to unforeseen circumstances, Dr. Arnold Monto will be unavailable to chair today's meeting. However, we are lucky enough to be able to have Dr. Stanley Perlman stand in as the chair of today's meeting. Dr. Perlman is Professor of Microbiology and Immunology, Professor of Pediatrics, and holds a Distinguished Chair at the University of Iowa, and his work focuses on coronaviruses. So I'll now turn the meeting over to Dr. Perlman.

Dr. Perlman: Thank you, Dr. Marks. I want to welcome everybody to the meeting. The members, the participants, and the public who's listening in this meeting is dealing with one important question and several important topics. And we have a very full agenda today. So our goal is to be both thorough and transparent in what we have to say. And with that, I'm going to turn this over to Sussan Padar, who's our Designated Federal Officer.

Administrative Announcements, Roll Call, & Committee Introductions

Dr. Paydar: Thank you, Dr. Perlman. Good morning, everyone. This is Dr. Sussan Paydar, and it is my great honor to serve as a Designated Federal Officer for today's 178th Vaccines and Related Biological Products Advisory Committee meeting. On behalf of the FDA and the Center for Biologics Evaluation and Research, CBER, and the committee, I'm happy to welcome everyone for today's virtual meeting. Today, the committee will meet in open session to discuss future vaccination regiments addressed in COVID-19. Today's meeting and the topic we're announced in the Federal Register Notice, which was published on December 19th, 2022.

At this time, I would like to introduce and acknowledge outstanding leadership of my Division Director, Dr. Prabhakara Atreya, and the excellent work of my team whose contributions have been critical for preparing today's meeting, Ms. Karen Thomas. Ms. Joanne Lipkind, and Ms. Lisa Johnson. I also would like to express our sincere appreciation to Mr. Derek Bonner in facilitating the meeting today. Also, our sincere gratitude goes to many CBER and FDA staff working very hard behind the scenes trying to ensure that today's virtual meeting will also be a successful one like all the previous BPAC meetings.

Please direct any press media questions for today's meeting to FDA's office of the Media affairs@fdamafda.hhs.gov. The transcriptionists for today's meeting are Catherine Diaz and Deborah Dellacroce from Translation Excellence.

We will begin today's meeting by taking a formal roll call for the committee members and temporary non-voting members. When it is your turn, please turn on your video camera, unmute your phone, and then state your first and last name, institution, and areas of expertise.

And when finished, you can turn your camera off so we can proceed to the next person. Please see the member roster slides, in which we'll begin with the chair, Dr. Stanley Perlman. Dr. Perlman?

Dr. Perlman: Hi, I am Dr. Stanley Perlman. I am a Professor of Microbiology and Immunology and Pediatrics at the University of Iowa, and my expertise is in coronaviruses.

Dr. Paydar: Great, thank you. Next is Dr. Paula Annunziato, non-voting member, our industry representative.

Dr. Annunziato: Good morning. I'm Paula Annunziato. I lead Vaccines Clinical Development at Merck. And as you just said, I am the non-voting industry representative for today.

Dr. Paydar: Thank you. Paula. Dr. Adam Berger.

Dr. Berger: Hello, I'm Dr. Adam Berger. I'm the Director of Clinical and Healthcare Research Policy at the National Institutes of Health. I oversee all of our clinical research and clinical trial policies. Thanks.

Dr. Paydar: Great. Thank you. Dr. Henry Bernstein, Hank.

Dr. Bernstein: All right. Here we go. Good morning, everyone. My name is Hank Bernstein. I'm a Professor of Pediatrics at the Zucker School of Medicine at Hofstra Northwell. My areas of expertise include pediatrics and vaccines. Thank you.

Dr. Paydar: Thank you, Dr. Bernstein. Dr. Archana Chatterjee.

Dr. Chatterjee:Good morning, everyone. My name is Archana Chatterjee. I have the honor and privilege to serve as Dean of Chicago Medical School and Vice President for Medical Affairs at

Rosalind Franklin University of North Chicago. My areas of expertise are in pediatrics and vaccines. I am trained as a pediatric infectious diseases specialist.

Dr. Paydar: Great. Thank you, Archana. Captain Amanda Cohn.

Dr. Cohn: Good morning, everyone. My name is Dr. Amanda Cohn. I am a Medical Epidemic Epidemiologist at the Centers for Disease Control and Prevention, and my expertise is in pediatrics and vaccines.

Dr. Paydar: Thank you, Amanda. Dr. Hayley Gans.

Dr. Gans: Good morning, everybody. It's great to be here. I am a Professor of Pediatrics at Stanford University and the Director of our Pediatric Infectious Disease program for immunocompromised hosts. My main area of focus for my research is on vaccine immunology. Thank you.

Dr. Paydar: Thank you, Hayley. Captain David Kim.

Dr. Kim: Oh, good morning, everyone. This is David Kim with the National Vaccine Program in the Office of Infectious Disease and HIV/AIDS Policy in the Office of the Assistant Secretary for Health. And I'm trained in internal medicine, with a particular in interest in in vaccine policy.

Dr. Paydar: Fantastic. Thank you. Dr. Paul Offit.

Dr. Offit: Yes, good morning. my name's Paul Offit. I am an Attending Physician in the Division of Infectious Diseases at the Children's Hospital of Philadelphia, and a Professor of Pediatrics at the School of Medicine at the University of Pennsylvania. And my expertise is in the area of vaccines, specifically mucosal vaccines. Thank you.

Dr. Paydar: Thank you. Dr. Steven Pergam.

Dr. Pergam: Thanks Sussan. I'm Steve Pergam. I'm a Professor in the Vaccine and Infectious Disease Division at the Fred Hutchinson Cancer Center. And my primary focus is on immunosuppressed patients and infections in population.

Dr. Paydar: Thank you. Dr. Eric Rubin.

Dr. Rubin: Good morning. I'm Eric Rubin. I'm an Infectious Disease Physician and researcher at Harvard, the Brigham and Women's Hospital, and the New England Journal of Medicine.

Dr. Paydar: Great. Thank you so much everybody. Next, we will do a roll call of our temporary voting members. Dr. Bruce Gellin is not here with us right now. He will join us shortly. Oh, you are in. Thanks. You made it on time. Perfect. Thanks so much for making it on time from another continent.

Dr. Gellin: It'll be a long day or a long night, but maybe for all of us. I'm Dr. Bruce Gellin. I'm currently a Senior Vice President at the Rockefeller Foundation. My training is in adult internal medicine infectious diseases, and I have spent half a career in vaccine policy. Thanks.

Dr. Paydar: Thank you, Dr. Gellin. Dr. Randy Hawkins, our alternate consumer representative. Dr. Hawkins.

Dr. Hawkins: Good morning. Randy Hawkins, pulmonary and Critical care of Medicine, and the acting consumer representative. I'm in private practice, pulmonary internal medicine, and on the faculty at Charles University of Medicine and Science.

Dr. Paydar: Great. Thank you so much. Dr. James Hildreth.

Dr. Hildreth: Good morning. I'm Dr. James Hildreth. I'm the President and CEO of Meharry Medical College and Professor of Internal Medicine. I'm an immunologist and I study the interactions between viruses and their hosts and how they cause disease. Thank you.

Dr. Paydar: Great. Thank you so much, Dr. Jeannette Lee.

Dr. Lee: Yes, good morning. My name is Jeanette 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, and my area of expertise is design and analysis of clinical trials. Thank you.

Dr. Paydar: Thank you, Janet. Next is Dr. Ofer Levy.

Dr. Levy: Hello, good morning. My name is Ofer Levy. I'm an attending physician in infectious diseases at Boston Children's Hospital and a Professor of Pediatrics at Harvard Medical School. I direct the Precision Vaccines Program, which is a multidisciplinary program to discover and develop vaccines tailored to vulnerable populations such as infants, immunocompromised hosts, those with comorbidities and older adults. Thank you.

Dr. Paydar: Thank you, Dr. Levy. Dr. Pamela McInnes.

Dr. McInnes: Morning. My name is Pamela McInnes. I'm a retired Deputy Director of the National Center for Advancing Translational Sciences at the National Institutes of Health. Thank you.

Dr. Paydar: Thanks very much, Pamela. Dr. Cody Meisner.

Dr. Meisner: Thank you, Dr. Padar. Good morning to everyone who was listening, my name is Cody Meisner. I'm a Professor of Pediatrics in Medicine at the Geisel School of Medicine and Dartmouth Hitchcock Medical Center. I am also a vaccine subject matter expert at barter within

the Department of Health and Human Services. I appreciate the opportunity to participate in today's meeting. Thank you.

Dr. Paydar: Thank you, Dr. Meisner. Next is Dr. Michael Nelson.

Dr. Nelson: Thank you. Good morning. I'm Michael Nelson, Allergist, Immunologist at the University of Virginia, where I serve as Chief of the Asthma, Allergy and Immunology Division, as well as President of the American Board of Allergy Immunology. My expertise is in vaccine adverse events and allergic and immunologic diseases. So thank you.

Dr. Paydar: Thank you so much. next is, Dr. Art Reingold.

Dr. Reingold: Good morning. I'm Art Reingold. I'm a faculty member at the School of Public Health at the University of California Berkeley with an interest in infectious diseases, particularly vaccine preventable diseases. Thank you.

Dr. Paydar: Great. Thank you. Next is Dr. Mark Sawyer.

Dr. Sawyer: Good morning. I'm Mark Sawyer. I'm a Professor of Pediatric Infectious Disease at the University of California San Diego. And my area of expertise are the public health aspects of vaccines. Thanks very much.

Dr. Paydar: Thank you. And last but not least, Dr. Melinda Wharton.

Dr. Wharton: Good morning. I'm an adult infectious disease physician who works in CDC's immunization program, and I work in vaccine program and policy. Thanks.

Conflict of Interest Statement

Dr. Paydar: Thank you. Great, thanks everyone. We have a total of 22 participants, 21 voting and one non-voting member. So now I'll proceed with reading the FDA Conflict of Interest disclosure statement for the public record. The Food and Drug Administration, FDA, is convening virtually today, January 26th, 2023, the 178th meeting of the Vaccines and Related Biological Products Advisory Committee, VRBPAC, under the authority of the Federal Advisory Committee Act, FACA, of 1972.

Dr. Stanley Perlman is serving as the acting voting chair for today's meeting. Today on January 26th, 2023, the committee will meet in open session to discuss future vaccination regimens addressing COVID-19. This topic is determined to be a particular matter involving specific parties, PMISP. With the exception of industry representative member, all standing and temporary voting members of the VRBPAC are appointed special government employees, SGs, or regular government employees, RGs, from other agencies, and are subject to federal conflict 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-USC Section 208 is being provided to participants in today's meeting and to the public. Related to the discussions at this meeting, all members, RGEs and SGEs, and consultants of this committee have been screened for potential financial conflict 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 the 18 US Code 208, their employers. Their interest may include investments, consulting, expert witness testimony, contracts and grants, cooperative research and development agreements, teaching, speaking,

writing, patents and royalties, and primary employments. 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 federal ethics and conflict of interest laws under 18-USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular government employees who have financial conflicts of interest when it is determined that the Agency's need for special government employee services outweigh 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 the services which the government may expect from the employee.

Based on today's agenda and all financial interests reported by committee members and consultants, there has been one conflict of interest waiver issued under 18 US Code 208. In connection with this meeting, we have the following consultants serving as temporary voting members, Dr. Bruce Gellin, Dr. Randy Hawkins, Dr. James Hildreth, Dr. Jeanette Lee, Dr. Ofer Levy, Dr. Pamela McInnes, Dr. Cody Meissner, Dr. Michael Nelson, Dr. Art Reingold, 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 the industry representative for today's meeting. Industry representatives are not appointed as special government employees and serve as non-voting members of the committee. Industry representatives act on behalf of all regulated industry and bring general industry perspective to the committee. Dr. Randy Hawkins is serving as the alternate consumer representative for this committee. Consumer representatives are

appointed of special government employees and are screened and cleared prior to their participation in the meeting. They are voting members of the committee.

We have a large number of federal and non-federal speakers, as well as some guest speakers today making various presentations on timely and relevant topics. The following speakers, guest speakers, and responders for this meeting have been screened for their conflicts of interest and clear to participate as speakers for today's meeting. They are: Dr. John Beigel, Associate Director for Clinical Research, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institute of Health, NIH, Bethesda, Maryland; Dr. Rituparna Das, Vice President, Clinical Development COVID-19 Vaccines, Moderna Incorporated, Cambridge, Massachusetts; Dr. Filip Dubovsky, Executive Vice President and Novavax Chief Medical Officer, Novavax, Gaithersburg, Maryland; Dr. Darin Edwards, Senior Director of Immunology Infectious Disease Group, Moderna Incorporated, Cambridge, Massachusetts; Dr. Jefferson Jones, Commander, US Public Health Service, Medical Epidemiologist, National Center for Immunization and Respiratory Diseases, Center for Disease Control, CDC, Atlanta, Georgia; Dr. Nicola Klein, Director, Kaiser Permanente Vaccine Study Center, Professor, Department of Health Systems Science, Kaiser Permanente, Bernard J. Tyson School of Medicine, Oakland, California; Dr. Ruth Link-Gelles, Lieutenant Commander, US Public Health Service, Epidemiologist, Division of Viral Diseases, National Center for Immunization and Respiratory Diseases, Center for Disease Control, CDC, Atlanta, Georgia; Antonella Lozito, PharmD, Executive Director, Regulatory Affairs, Infectious Disease, Moderna Incorporated, Cambridge, Massachusetts; Dr. Heather Scobie, Surveillance and Analytics Team Lead, Acting, National Center for Immunization and Respiratory Diseases, CDC, Atlanta, Georgia; Dr. Tom Shimabukuro, Deputy Director H1N1 Vaccine Force

Immunization Safety Office, CDC, Atlanta, Georgia; Dr. Kena Swanson, Vice President, Viral Vaccines, Vaccine Research and Development, Pfizer Incorporated, New York, New York.

Disclosure of conflicts of interest for speakers, guest speakers, and responders follows 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 that they may have with any affected firms, its products, and if known, its direct competitors. We would like to remind standing and temporary members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need 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 acting chair, Dr. Perlman. Thank you. Dr. Perlman.

Dr. Perlman: Thank you, Dr. Padar. And so now I will turn the meeting over to Dr. Peter Marks, who's the Director for the Centers for Biological Evaluations and Research, for his introductory comments.

FDA Introduction

Welcome

Dr. Marks: Thanks very much, Dr. Perlman. Before spending a few minutes introducing today's topic, I want to first take a few moments in re remembrance of Dr. Oveta Fuller. She was a temporary voting member of the committee during the entire course of the coronavirus outbreak through its last meeting. And sadly, she died on November 18th, 2022. Dr. Fuller was a distinguished virologist at the University of Michigan School of Medicine who focused her work on herpes virus entry and pathogenesis and translational research for HIV and AIDS elimination. She was dedicated to global public health and to health equity interventions to reduce infections in chronic diseases. We will sincerely miss her contributions to the committee, and our thoughts are with her friends and family.

Next, I'd like to introduce Dr. David Kaslow to people. He started at FDA this past October as the Director of our Office of Vaccine Research and Review. Dr. Kaslow comes to CBER from PATH, where he served as the Chief Scientific Officer for Essential Medicines and the head of PATH Sensor for Vaccine Innovation and Access. He previously served as the Vice President of Vaccines in Infectious Disease at Merck Research Laboratories, where he also served in advisory positions with MVII and the Bill and Melinda Gates Foundation. And prior to these positions, he founded the Malaria Vaccine Development Unit at NIH. And since coming to the Agency, his scientific expertise and leadership have already distinguished him, and he will transition to running the Vaccine and Related Biologics Products Advisory Committee meetings in the future for the FDA side.

And finally, I just want to take a few minutes to introduce today's topic of future vaccination regimens addressing COVID-19. It's simply a fact that the authorized and approved COVID-19 vaccines have helped to significantly reduce the morbidity and mortality from SARS Coronavirus II. That said, these vaccines were developed in record time during a period in which

we were, and which we continue to be, learning more about SARS Coronavirus II, not just about the virus, but also how it causes disease, and especially how rapidly it can evolve. Because of its rapid evolution, we've needed to adjust our approach over time. And we're now in a reasonable place to reflect on the development of the COVID-19 vaccines to date, to see if we can simplify the approach to vaccination in order to facilitate the process of optimally vaccinating and protecting the entire population moving forward. And so, that's under discussion today. So, with that I will turn this back over to the chair.

Dr. Perlman: Thank you, Dr. Marks. Now I'd like to introduce Dr. Kaslow, who's already been mentioned. He's the director of the Office of Vaccines Research and Review at the Center for Biologics Evaluation and Research, and I would ask him to have any introductory comments.

Considerations for Updating Boosters and Whether and How Primary COVID-19 Vaccine Strain Composition Should Be Modified

Dr. Kaslow: Thank you Dr. Perlman. And thank you Dr. Marks for very, very kind introduction. It is an honor to join this 178th meeting of VRBPAC for the first time as Director of OVRR. And as Dr. Marks noted, this is a consequential meeting to determine if we've reached a point in the pandemic that allows for simplifying the use of current COVID-19 vaccines, and if it is the moment to implement a more routine approach to periodically updating the strain composition of these vaccines. To frame today's discussion, I'd like to start by re-reviewing the current state of these two topics and ideally where we would like to be going in the future. Next slide, please.

Currently, as Dr. Marks noted, there's over a dozen different COVID-19 vaccine presentations and several different immunization schedules authorized or approved in the United States, leading to complexities in implementation, use, and communication. In the future, ideally, the same COVID-19 vaccine strain composition would be used for both primary series and boosters, and in future periodic vaccine campaigns, a much simpler immunization schedule would be used, perhaps based simply on age, with a few risk-based adjustments, as will be proposed in a few slides. Next slide, please.

As you'll hear in several presentations today, the virus continues to evolve rapidly, and revaccination with an updated vaccine has been shown to restore protective immunity. Going forward, FDA envisions an evidence-driven approach, similar in many ways to the process used for influenza vaccines, to monitor and update as needed the composition used in all COVID-19 vaccines, with the goal to induce or restore protective immunity through these periodic vaccination campaigns. Next slide, please.

So with that framing in mind, FDA asked VRBPAC today to consider the following topics, simplification from three perspectives. First, transitioning to the same vaccine strain composition for primary series and booster vaccination. Second, harmonizing the strain composition of all COVID-19 vaccines, be it mRNA or protein-based, for example. Third, simplifying the immunization schedule for future vaccination campaigns to administer one dose for most adults, adolescents, and older children, and for young children who were previously immunized, and potentially additional doses for high risk, older adults and persons with compromised immunity and young children who have not been previously immunized. We'd also like VRBPAC to consider establishing a process for vaccine strain selection recommendations. Again, similar in many ways to that used for seasonal influenza vaccine, based on prevailing and

predicted variants that would take place by June to allow for vaccine production by September. And importantly, if there is a need, convening an ad hoc VRBPAC meeting to address highly pathogenic escape variants. Next slide, please.

The next three slides show at a very high level what is envisioned in the approach to periodic updating of vaccine strain composition. Shown on this slide is a proposed continuous and iterative three-step process in which integrated data are reviewed to determine the need for an updated composition recommendation, while in parallel and at risk updated vaccine candidates are evaluated so that if and when a recommendation is made, manufacturers can submit to FDA a timely data package of their updated vaccines for review. In the third step, real world evidence of the newly updated vaccine's effectiveness is collected and analyzed, which also starts the next three step process. Next slide, please.

Shown on this slide are the types of evidence that FDA would like to see generated and integrated as part of step one and three. This includes continuous epidemiologic clinical and viral surveillance, continuous viral characterization at the gene, phenotype, and antigen level, and as mentioned on the last slide, vaccine effectiveness studies on each subsequent updated vaccine. An integration of these data would be used by VRBPAC to recommend a strain change. Next slide please.

Shown on this slide are the typical types of data that would be submitted and reviewed in step two. Dr. Weir will review this in more detail in his presentation. Suffice it to say that FDA anticipates reviewing a comprehensive data package that may include manufacturing, nonclinical, and clinical data to authorize or approve an updated vaccine. Next slide please.

The final topic we're asking VRBPAC to discuss and is an approach to simplifying the immunization schedule to be used in future periodic vaccination campaigns. An example of a potentially simplified immunization schedule was provided in the briefing document. Shown here for discussion is the underlying concept, which is: presumably at this point in the pandemic, most of the general US population have been sufficiently exposed to spike protein, either to infection, vaccination, or both, such that a single dose of a COVID-19 vaccine would induce or restore vaccine effectiveness. As you will see, some preliminary age-based data that suggests which age groups might fit into this category. As with the influenza immunization schedule, it is also possible that some risk-based adjustments to the immunization schedule may be necessary. It could be that more than one dose is needed, high risk older adults, persons with compromised immunity, and young children who have not yet been completely immunized. At this time, those risk-based adjustments remain to be determined. Next slide.

Before reviewing the voting questions and discussion topics, I'd like to just briefly review today's agenda. We'll start with a series of informational presentations. First from CDC on the current epidemiology and an update of circulating variants. Also from CDC will be an update on bivalent vaccine effectiveness and safety, followed by FDA's update on bivalent vaccine effectiveness and safety. And then end the first session this morning with a presentation from NIH on improved generation COVID-19 vaccines. Next slide, please. Oh, next slide please. Thank you.

After a short break, we'll next hear from Moderna, Pfizer, and Novavax on their vaccines. And after lunch will be the Open Public Hearing session, followed by FDA's presentations on the topics under consideration by VRBPAC. After a short break, there will be an additional question

and answer session on the presentations, after which the committee will turn to the voting question and then the two discussion topics. Next slide, please.

The voting question is directed at simplifying the use of current COVID-19 vaccines. FDA asks VRBPAC: does the committee recommend harmonizing the vaccine strain composition of primary series and booster doses used in the United States to a single composition? For example, the composition for all vaccines administered currently would be a bivalent vaccine with an original plus Omicron BA.4/BA.5 composition. Next slide please.

After voting on the question, VRBPAC is asked to discuss two topics. The first on periodic updates to COVID-19 vaccines for use in future vaccination campaigns. Please discuss and provide input on the consideration of periodic updates to COVID-19 vaccines strain composition, including to the currently authorized or approved vaccines to be available for use in the United States in the fall of 2023. Next slide, please.

The second topic is on simplification of the immunization schedule. Please discuss and provide input on simplifying the immunization schedule to authorize or approve one dose for most adults, adolescents, and older children, and for young children who were previously immunized, and an additional dose for higher risk older adults, persons with compromised immunity and young children who have not been previously immunized. And with that, I'll turn the floor back to our chair, Dr. Perlman.

Q & A

Dr. Perlman: Thank you, Dr. Kaslow. So we have seven minutes now for questions from the committee. I see one hand this up. Dr. Meissner.

Dr. Meissner: Thank you Dr. Perlman. And thank you Dr. Marks and Dr. Kaslow for your comments. I have one comment and one question. First, I wanted to thank the FDA and all the workers at, your colleagues at CBER who put together the FDA briefing document. That's just an enormous amount of work and thank you for bringing that into one package. The question I have for you, Dr. Kaslow, is: is it reasonable to make the decision in June in regard to composition of the vaccine for the following fall? That's obviously a much shorter time than the influenza vaccine, which is selected typically in February. Now it's a different vaccine platform of messenger RNA for the COVID-19 vaccines. But is that a reasonable goal? Over.

Dr. Kaslow: Thank you, Dr. Meissner, for the comments on the backgrounder and also for the question. I think that you're going to hear in the presentations today more detail on the process, the manufacturer's perspective on the feasibility of that, as well. And so I think we should maybe come back to that question, particularly after Dr. Weir's discussion this afternoon, or presentation this afternoon, where I think we'll go through a bit more of the detail that's involved in getting us there. But thank you for the question.

Dr. Meissner: Thank you.

Dr. Perlman: Dr. Levy.

Dr. Levy: Hi, Ofer Levy, Precision Vaccines Program, Boston Children's Hospital. Again, thanks to Dr. Kaslow, and I second Cody Meissner's comments on the FDA briefing documents, which were excellent. In the background just provided, a rationale was set for harmonizing, simplifying the approach, which makes good sense. and then an example was given, eg, using the bivalent vaccines, as the yearly booster, or yearly vaccine. And I just wanted to know

whether FDA is framing today's discussion to consider other options or emphasizing that option. I'm just trying to understand how this is being framed in terms of background. Thank you, Dr. Kaslow.

Dr. Kaslow: Thank you, Dr. Ofer. Yes. No. Indeed, that this is being framed as a discussion topic. Certainly not a, a voting topic. And the Agency is quite interested in the input from the advisory committee on this topic.

Dr. Perlman: Okay. Thank you. Dr. Reingold.

Dr. Reingold: Yeah. Hi. I'd certainly like to second the comments about the briefing document. Thank you to all the FDA staff. I just want a question that follows up a little bit on Dr. Meissner's question, which is, I think beyond the question of how long would it take companies to produce a vaccine, the other question is when it would be optimal to administer it. And whether we're talking about trying to start administering a vaccine in September or October or November clearly might depend in part on how long we think the protection will last and what we think the — when most infections and illnesses would be occurring. So, I think we need to at least think about when the optimal time for administering the vaccine is as well. Thank you.

CDC Presentations

Dr. Perlman: Okay, thank you. And we, I think now we can move on to the presentations, since there's no more questions at the moment. So if Dr. Scobie is ready, I will introduce her. She is the Surveillance and Analytical Team Lead and the at the National Center for Immunization and

Respiratory Diseases of the CDC. And she's going to give us an update on the current epidemiology of the COVID-19 pandemic and its SARS-CoV-2 variants.

Update on Current Epidemiology of the COVID-19 Pandemic and SARS-CoV-2 Variants

Dr. Scobie: Good morning. Can you hear me?

Dr. Perlman: Yes.

Dr. Scobie: Okay, next slide. This stack bar graph shows recent US trends in the national weighted estimates of variant proportions and nowcast projections of circulating SARS-CoV-2 lineages by week of specimen collection. The various Omicron sub-lineages have been over 99% predominant for many months now. For the week ending January 21st, XBB.1.5 in dark purple comprised49.1% of sequences, BQ.1.1 in teal was 26.9%, BQ.1 in dark green was 13.3%, and XBB in lavender was 3.3%. Several other BA.2, BA.5, and BA.4 related lineages are 2% or less. Next slide.

This map shows the relative proportions of the Omicron sub-lineages across the 10 Health and Human Services regions. During the most recent week, XBB.1.5 in dark purple represented the majority of circulating lineages in regions one, two, and three on the east coast, while BQ.1.1 in teal and BQ.1 in dark green represented the majority of circulating lineages in other US regions. Next slide.

This is a summary of the various circulating Omicron sub-lineages. 44% of circulating sub-lineages in the US are related to BA four or b A five sub-lineages, which have the same

spike protein that was included in the updated bivalent vaccine, and the remainder is attributed to BA.2 related lineages. Although we have many different named lineages and circulation, most of these newer sub-lineages differ by only a few amino acids in the receptor binding domain from their parental sub-lineage, while XBB.1.5 in the bottom right has the highest number of mutations among this group. We also see evidence that these strains are co-evolving the same mutations, which in some cases, as shown in red, are known to impact monoclonal antibody treatments and likely contribute to partial immune escape more generally. Next slide.

These are recent CDC data on the neutralizing activity of sera after receiving a monovalent booster, in the top panel. The ancestral strain is shown in dark blue on the left end. Different Omicron lineages are pictured in various colors on the to the right. The more recent variants are on the far left: BQ.1.1 in lavender, XBB in red, XBB.1 in pink, at the largest relative decreases in neutralization. The bottom panel shows the neutralizing activity of sera after receiving a bivalent booster and a total of four vaccine doses. Neutralization of all Omicron sub-lineages relative to the ancestral strain was notably improved after the bivalent booster, but XBB and XBB.1 still had the largest reductions in neutralization. A new publication from Ohio State University has shown equivalent neutralization of XBB.1.5 by bivalent booster sera relative to XBB and BQ.1.1. Next slide. Next slide.

As of January 18th, there have been almost 101.9 million COVID cases reported in the US and almost 1.1 million reported COVID-19 associated death. Next.

This graph shows the weekly trends and reported numbers of COVID-19 cases overlaid with the weekly test percent positivity, which is a marker of transmission intensity. The trends aligned remarkably well in late 2020 through early 2022, but became uncoupled starting in May 2022, related to decreases in provider-based testing and increases of at home testing. For this

reason, cases reported to surveillance are underestimated. This month, after increases in November, December 2022, case counts and test percent positivity are starting to show decreasing trends, suggesting decreases in overall transmission. Next slide.

These are the trends in age specific rates of COVID-19 cases over time. More recently, case rates have been higher in older ages, in purple and pink, relative to younger ages, in blue and yellow colors, compared with earlier in the pandemic. However, this may be related to differences in laboratory testing practices by age. Next slide.

These are trends in the percent of emergency department visits attributed to patients diagnosed with COVID by age group from syndromic surveillance. Percentages have been decreasing in recent weeks but were highest in children ages less than two years, in yellow, and older adult ages 75 plus years, in the purple dotted line, and 65 to 74 years, in pink. Next slide.

These are weekly trends in adult COVID-19 associated hospitalization rates by age group from COVID-NET. Higher hospitalization rates have always occurred in the 75 plus year age group in purple, followed by people ages 65 to 74 years in red, 50 to 64 years in pink, and 18 to 49 years in blue. On the right, you can see that since April, hospitalization rates have increased more in older age groups, especially for 75 plus years compared with younger adults. Next slide.

These are COVID-19 associated hospitalization rates among children by age group. Pediatric hospitalization rates were relatively low during the first year and a half of the pandemic but increased during the Omicron surge, especially for infants less than six months of age, in red, were not eligible for vaccination, and children ages 6 to 23 months in orange, who became eligible for vaccination in June, 2022. COVID-19 hospitalization rates have remained highest in these two youngest age groups relative to children in older age groups. Next slide.

These are weekly trends in the COVID-19 associated mortality rates reported from case surveillance by age group. The data show that higher mortality rates are consistently observed in older age groups. Most notably on this graph, among those aged 75 plus, 65 to 74, and 50 to 64 years, as shown in the purple and pink colors. Since April, we have observed decreased death rates in younger ages relative to older age groups, especially people ages 75 plus years. Next slide.

This is a summary table of the cumulative incidents of cases and deaths by age group during the Omicron variant period of January 2nd, 2022, to January 18th, 2023. On the left, case incidence was relatively even across age groups with some variation likely related, in part, to differences in at-home testing practices by age. On the right, death rates increased with increasing age among the adult age groups. Higher death rates were also observed for infants less than one year of age than in other pediatric age groups. However, this table does not separate out children younger than six months who are not eligible for vaccination. Next slide.

This is a summary table from COVID-NET of cumulative incidents of hospitalizations by age group during the Omicron variant period, so January 2nd, 2022, to January 14th, 2023. I note that there's a typo in the title there. Sorry about that. Here again, we see a pattern of higher hospitalization rates with increasing age and also among younger ages, most notably ages 65 to 74 and 75 plus years, and ages less than six months, which were on the same order of magnitude. Children 6 to 23 months were also increased relative to older children. Next slide. Next slide.

As of January 18th, over 229.5 million people in the US have been vaccinated with a primary series, which is 73% of the population ages five years and older. Since first being authorized on September 1st, 2022, 50.6 million people have received an updated bivalent booster dose, which is 60 16% of the population ages five years or older. Next slide.

These data show trends over time and by age group and the percentages of people who have received at least a primary series on the left, and an updated bivalent booster dose on the right. In both figures, vaccination coverage is higher in older age groups, indicated in purple and pink colors. On the left, we can also see that children under the age of 12 years in the yellow colors, who became eligible for vaccination more recently, have the lowest coverage for the primary series. Coverage with the updated booster dose on the right is highest for the 65 plus age group in purple, followed by 50 to 64 years in pink, and younger adults in the blue colors. Next slide.

This is a summary table of COVID-19 vaccination coverage by age group and dose opportunity. On the left, children ages less than two and two to four years became eligible for vaccination most recently. So they've had the fewest vaccination opportunities. They have the lowest coverage, and 90% or more of these groups are unvaccinated. On the right, adults aged 65 plus and 50 to 64 years, were at highest risk of severe disease, have been targeted with the most vaccination opportunities, have the highest coverage, and only 5% of these groups are estimated to be unvaccinated. The other age groups in the middle reflect a gradation between these two extremes. Next slide.

This is sera prevalence data reflecting categories of vaccine and infection history among US adult blood donors overall on the left, and by age group on the right, for two surveys conducted in the first and second quarters of 2022. As expected, increasing proportions of vaccine-induced immunity only, in blue, and both vaccine and infection induced immunity, in green, were observed in older age groups, while higher proportions of infection induced immunity only, yellow, were observed in younger adult age groups. During the second quarter survey, as shown in slightly darker shades, proportions of adults with both vaccine and infection

induced immunity increased across all age groups. I note that the most recent data presented here are for June 2022. Next slide.

This is pediatric sera prevalence data from a national survey of commercial laboratory specimens by age group from March to December 2022, including new unpublished data. On the left is infection induced sera prevalence, which was noticeably lower for children ages 6 to 11 months in light blue and children ages 12 to 23 months in green than in older age groups. On the right is combined sera prevalence for infection and vaccine-induced immunity, which was higher overall. However, combined sera prevalence was still lower for infants ages 6 to 11 months and children ages 12 to 23 months. Next slide. Next slide.

This graph shows age adjusted rates of COVID-19 associated hospitalizations by vaccination status and receipt of a booster dose. Hospitalizations for COVID-19 have consistently been higher among unvaccinated than vaccinated people over time. In November, adults ages 18 years or older and vaccinated with a bivalent booster had 16 times lower risk of COVID-19 associated hospitalization compared to unvaccinated people, and 3 times lower risk of COVID-19 hospitalization compared to vaccinated people without a bivalent booster. Next slide.

For cases diagnosed in November 2022, people ages 5 years and older with a bivalent booster had 13 times lower risk of dying from COVID-19 compared to unvaccinated people and 2 times lower risk of dying from COVID-19 compared with vaccinated people without a bivalent booster. These data suggest that getting an updated COVID-19 bivalent booster can enhance protection that might have decreased over time related to immune escape of variants or waning immunity and time since receipt of the last monovalent dose. Next slide.

Unvaccinated people are at much higher risk of severe COVID-19 illness than vaccinated people. Most vaccinated people who get severe COVID-19 illness have multiple risk factors, including older age and underlying conditions like immunosuppression, diabetes, and chronic kidney, lung, cardiovascular, and/or neurologic diseases. Antiviral drugs can help reduce the risk of severe illness in people at higher risks. Next slide.

In summary, CDC continues to monitor emerging variants like the sub-lineages of Omicron, including their prevalence and impact on disease incidence, severity, and vaccine effectiveness over time. Variant variation has occurred in rates of severe illness related to community transmission and emerging variants. However, an increasing proportion of severe illness over time has occurred in older adults, especially ages 75 plus years and infants and children less than two years. There has been an increase in both vaccine-derived and infection-acquired immunity for all age groups, but susceptibility in children less than two years remains. It's important to stay up to date with vaccination, including receipt of updated bivalent booster doses in eligible populations to protect against severe COVID-19 illness. Therapeutics and multiple prevention measures should be used to protect people at higher risk of severe COVID-19 illness regardless of vaccination status. Next slide.

I'd like to thank the following people and organizations. Thank you.

Q & A

Dr. Perlman: Thank you, Dr. Scobie, for a really clear and informative presentation. And we have 15 minutes for questions. And before we start, I just want to make one comment. I wonder

if the using neutralizing antibodies as the sole correlative protection, which is what we kind of do, may need to be upgraded or changed the bit, because it seems like people are still pretty well protected, even though the antibody titers are very low to the newest variants. So with that, I will take the first question. Dr. Gans.

Dr. Gans: Thank you very much. Thank you for that wonderful, presentation Dr. Scobie. I had a couple of questions. You showed us the variant range over our geographic area in the US for one single time point. And I'm wondering if it would be more helpful, and maybe we're hearing this at some point, to look at the trends because, as we know, strain variability does start in one location and then often wander over through the geographic areas as there's a different rate of disease in these areas. And this is important just because we have to understand, if there is a notion to change based on some evidence, are these geographic variations, which we actually see globally, going to change and catch up with anything that we would consider, or are they going to stay stagnant? I think the answer to that is the first one.

And my second question, and then I'll mute myself. We have this notion that severe disease can be impacted by the medications that we currently have available, but we should be very mindful that many of these medications are not available for children. So we need to sort of talk about that and consider that. And my last comment was the same as Dr. Perlman's. I think we need to get away from neutralizing antibody titer measures as a marker of efficacy. Thank you.

Dr. Scobie: Thank you. So I think, I mean, well one, in terms of the regional variation, those graphs can be viewed by, or charts with the maps, can be viewed by week, if you're interested in regional variation, on the CDC's COVID data tracker. But, early on, before Delta became the predominant circulating lineage, we did observe regional circulation of a few lineages, but never

kind of reached predominance in the United States. An example might be like Epsilon, which was circulating on the West coast. But since then, what we've observed is that, if a variant has some sort of advantage, that it's generally taken over and swept across the country no matter where it's first detected. And I think there's reasonable suspicion that that will probably occur with XBB.1.5 as well. So it's more or less just a matter of time, but I guess time will tell. We're in, of course, a new era with variance with this so-called variant soup. We don't have a great term for it, but it's a collection of B.5, BA.4, and BA.2 related lineages. And, as I noted, they often just differ by, one or two amino acids from each other, which has been one reason where we haven't for a while had a clear kind of winner in terms of selective advantage. but it's seeming like with XBB.1.5, we're at that place now.

Dr. Perlman: Hey, thank you. Dr. Hawkins.

Dr. Hawkins: Thank you very much. Dr. Scobie, I apologize if you answered this question. My question surrounds home testing and the impact on variant composition data. You advised us that COVID-19 infection is underestimated because of things like home testing. So how are home test results incorporated into this composition data, variant data that is?

Dr. Scobie: So, home test results are definitely not incorporated into genomic surveillance at this point. There's no framework for testing those home test specimens for sequencing. There are efforts, like my Make My Test Count, which is a government effort where you can report your home test results. And there's a website, and I believe you can see the results through that website. And CDC is working to make those data available publicly. I know that's either imminent or has already posted. But that's a separate issue in terms of making those data available as part of surveillance and validating whether they work as a surveillance measure that

we can follow over time. But you're right in that, in pointing out that that framework isn't included in terms of what we test currently for genomic sequencing, which is limited to swabs.

Dr. Hawkins: And we think that this is not a significant factor?

Dr. Scobie: Well, if you're worried, I mean, people who do home tests in general are not — they're either before the point of care seeking, or they have less severe cases, or they're doing asymptomatic screening for whatever reason because of contact. So if we were worried about catching all of those people and what's circulating among those more mild cases, I would say we have a problem. But I guess I don't think that that's a problem, that we're only focused on swabs, which are generally for people either seeking care because of more severe illness or because they need to confirm that their lab — the test they ran at home is correct. So I don't think that it's a problem that we're not catching them in genomic surveillance.

Dr. Hawkins: Thank you.

Dr. Perlman: Thank you. Dr. Gellin?

Dr. Gellin: Yeah, thanks. Thanks a lot, Heather, for all of that. My question's derived really bit from Dr. Perlman and Dr. Reingold's question about the timing, and really, duration of protection. What assumption are we using for how long after vaccination people are protected? Because that obviously will have implications for when we think they need to get more protection. Thanks.

Dr. Scobie: And do you mean protected against infection or protected against severe illness? I think that there are differences there and we need to be clear.

Dr. Gellin: Okay, then maybe you should put both on the table.

Dr. Scobie: Okay. I mean, Dr. Link-Gelles is going to speak next and is going to show data that speaks to this, but I think in general we're saying that the vaccines protect for, up what protects pretty well for up to three months against infection and much longer for severe infection. And that Dr. Link-Gelles should be able to speak to that better.

Dr. Perlman: Dr. Meissner.

Dr. Meissner: Thank you, Dr. Perlman. And thank you, Dr. Scobie, for a very thoughtful and thorough presentation. I would like to ask a question that I think we've discussed once before. I live in the state of Massachusetts, and the Massachusetts Department of Health reports every Thursday on the number of patients who are hospitalized with a positive assay and who are hospitalized because of COVID symptoms. And last January 17th, they reported there were 1060 patients in Massachusetts hospitalized with a positive assay, but only 349, or 33%, were hospitalized because of COVID symptoms. I think that's becoming increasingly important as we move into an era where these variants are clearly more infectious and cause more asymptomatic disease. And if we're going to introduce vaccines that have a novel composition or have altered schedules for administration, it would be very helpful to know not who's hospitalized with an assay, because that doesn't tell us a great deal. What we want to know is who is hospitalized because of symptoms due to COVID-19 and is it possible for the CDC to generate that data? Because there's no reason that Massachusetts, it seems to me, would be any different than any other state. So it suggests that your rates are three times higher than the actual rates. Over.

Dr. Scobie: So the COVID-NET system, which is a hospital-based system, they've published papers that have shown, like you're saying, that people, using an algorithm that looks at diagnoses and divides people out based on just likely scenarios, you know, are you there for obstetric care, are you there for an accident, things like that. They're able to provide a percentage

of cases that they think are there, not because of COVID, but just with COVID, and they have shown that that has increased over time. So they usually provide that breakout in their publications.

It's not broken out in the surveillance data that's reported online. But they do use a reasonable case definition, which is essentially that people who've tested positive in a reasonable amount of time before admission or within several days after admission are basically a call to COVID-associated case. And those are the, the data that I presented to you today. So I think it's a reasonable thing to raise. But the trends that we're seeing are real and that the cases are older over time and generally have more underlying conditions. And yeah. So, those publications exist and address your concerns, I believe.

Dr. Meissner: Good. I agree with you that the trends are probably accurate. My concern relates to the absolute numbers. Because Massachusetts, they, if a patient's not getting dexamethasone or is not being treated for COVID disease, then it's unlikely that's that patient is hospitalized. So if the CDC incorporates those into their rates, I think that would be very helpful. Thank you.

Dr. Perlman: Dr. McInnes.

Dr. McInnes: Thank you, Dr. Scobie. My question is going back to your earlier data on, 100 — let me put my video on, yeah — back to 101.9 million cases at this stage. And so I just wanted a little clarification here. It wasn't clear to me, went quickly, about what the cases' attainment was. So this is detected by measurement, is that correct? It's not an assumption?

Dr. Scobie: So these are cases reported to CDC. I believe you're referring to that slide that just shows —

Dr. McInnes: It was an early slide. So, if you, and I know you don't like to speculate, you like to see, look at the data. But if these are measured cases, if this case ascertainment is by measurement and a positive result, what do you speculate the non-symptomatics are that have not appeared for medical care? I'm trying to get a sense of what percentage of the population might have been exposed to COVID, because it affects our discussion around hybrid immunity.

Dr. Scobie: Yeah. Well, I did present to speak to your point. I did. Okay. I did present the sera prevalence data, which is the most reasonable assessment that we have about people who've been exposed to infection. So those data address that and show that at this point, the majority, the vast majority of the US population has either been exposed to infection or vaccinated or both. So those sera prevalence data were presented and we could revisit that if you'd like.

Dr. McInnes: Okay. So when you say vast majority, sorry, what do you mean?

Dr. Scobie: Over… we can, let's see. We can go to that slide, but it's over 90 —

Dr. McInnes: Sorry, it went very quickly.

Dr. Scobie: If Jefferson Jones is on the line from CDC, Dr. Jones, he may want to intervene and speak to the sera prevalence data.

Dr. McInnes: Thank you.

Dr. Jones: Yeah. Thank you. So, on slide 21 was presented, although the data are slightly old at this time, in quarter two of 2022, there had been 22% of adults that had infection only induced immunity and 37% with hybrid immunity. So roughly 60% that had been infected, as evidenced by nucleocapsid and antibody positivity. And that likely is continued to increase, although the

numbers do differ quite a bit by age. And please let me know if you have any specific questions. So if you're looking at just the total numbers that have been infected —

Dr. McInnes: Yes.

Dr. Jones: Then you would sup the yellow and the green, which is an infection and hybrid immunity combined.

Dr. Scobie: So 59%, it looks like, would have been infected in quarter two of 2022, and a total of 94% have evidence of either having been infected or, having been infected and vaccinated, or vaccinated alone.

Dr. McInnes: So, the bottom line would be over 90% have either been infected or had vaccine or an infection. Is that correct?

Dr. Jones: That's correct. And that's been correct since the end of 2021, really, as far as either infected or vaccinated.

Dr. McInnes: So really no change in trend?

Dr. Jones: If you're just, I mean — there's big changes in trend in how many of hybrid immunity versus infection over time, as the number of people getting infected does accumulate. Particularly, and we're only able to talk about first infections, as this data can't speak to re infections.

Dr. McInnes: Right.

Dr. Jones: But it is likely that cases are increasingly, unable to detect the number of infections, both primary and reinfections. But the number of people that have any immunity from infection or vaccination has not greatly changed over the last year, as most people were either

infected or vaccinated. But as you'll see in the next presentation, recent vaccination or recent, it won't be — recent infection won't be presented, but recency of infection or vaccination does have a substantial effect on protection against infection, and to a lesser extent, the degree of protection against severe disease, as well.

Dr. McInnes: Thank you very much.

Dr. Perlman: Okay. Thank you. I think we probably need to move on. I know there's other people have questions and there'll be time later to address those questions, but I think we need to move on to the next presentation by Dr. Link-Gelles, who's the COVID-19 Vaccine Effectiveness Program Lead.

Update on Original COVID-19 Vaccine and COVID-19 Vaccine Bivalent Effectiveness and Safety

Dr. Link-Gelles: Good morning. Today I'll be presenting a summary of vaccine effectiveness data available from CDC studies and platforms, including vaccine effectiveness of both the original monovalent vaccines and updated bivalent vaccines. Next slide please.

I will first present estimates of vaccine effectiveness, or VE, of monovalent vaccines for symptomatic infection in young children. I'll then show early estimates of bivalent vaccine effectiveness for symptomatic infection due to XBB and its sub-lineages, as presented in yesterday's MMWR from CDC. Finally, I'll provide updates on VE of bivalent vaccine against severe disease in older adults. Next slide.

Starting with VE for symptomatic infection in young children, ages six months to five years for Moderna, and six months to four years for Pfizer BioNTech. Next slide.

So first, to orient everyone to the current recommendations: for younger children, two doses of Moderna vaccine are recommended four to eight weeks apart for the primary series. August 1st was the earliest date that a child could have been considered to have a complete series; in other words, at least two weeks after completion of their second dose. If receiving the Pfizer BioNTech vaccine, the primary series is three doses, with a first and second dose separated by three weeks, and the second and third doses separated by eight weeks. Since the series required an extra dose, the earliest date a child could have been considered to have a complete primary series was September 19th. For Pfizer, the third dose was changed to bivalent dose on December 9th, but the analysis that I'll present today were restricted to monovalent doses only. Next slide.

For background, I'm sharing the national coverage estimates from CDC's COVID data tracker for the primary series among children, shown in the red box in the middle of the slide. Note that this age group has the lowest coverage for either a single dose or a completed primary series, at just under 10% for one dose and just over 5% for the complete primary series in children aged two to four years. Low coverage can cause VE estimates to estimates to fluctuate somewhat, as those vaccinated early may be meaningfully different from those that remain unvaccinated. And these estimates that I'll show in a few minutes should be considered preliminary. Next slide.

The increasing community access to testing, or ICAT, platform includes community-based testing data from pharmacies and laboratory partners nationwide. It uses a test negative design with self-reported vaccine history at the time of the test registration. And for this analysis,

only children whose caregivers reported symptoms and who were between the ages of three and five for the Moderna analysis and three and four for the Pfizer analysis were included. And this is because pharmacies generally only test children ages three and up. Children with immunocompromising conditions were excluded. Data presented here for tests from July 4th, 2022, through January 17th, 2023, although the start date varies depending on the dose being analyzed,. This was a period when the Omicron BA.4 and BA.5 sub-lineages predominated, though include some time periods when XBB was also prominent. Next slide.

So starting first with Moderna estimates for children ages three to five years. Here we see preliminary estimates for VE against symptomatic infection for the monovalent Moderna vaccine series. On the top we see a VE of 47% for one dose or a partial series during the interval between the first and second dose. On the bottom is VE for the complete two dose primary series of Moderna, with an overall VE of 57% during the two weeks to three months after the second dose. These estimates are fairly similar to older children and adults against symptomatic infection. Next slide.

Moving on now to the Pfizer estimates. Here we see the same graphs, this time for Pfizer in children ages three to four years. On the top, for a one dose partial series, we see a VE of 12% with confidence intervals crossing the null. For two doses, which for Pfizer is also just a partial series, VE was 39% in the two weeks to three months after the second dose. And note that we did not have enough statistical power in this analysis to estimate VE for a three dose or complete series of Pfizer. Confidence intervals were too wide and did not meet precision thresholds for interpretation. Next slide.

I'll now move on to present early estimates of VE for a bivalent booster dose against symptomatic infection with the XBB and its sub-lineages. Next slide.

This is again using the national pharmacy testing data through the ICAT platform. I've highlighted the differences between the methods for this analysis and what was previously shown. Here, We're looking at adults with COVID-like illness, so that's one or more COVID-like symptoms, tested at one laboratory partner that had S-gene target data available. Variant was determined using S-gene target reduction, or failure, as a proxy for infection with BA.5 related sub-lineage. And S-gene target presence was used as a proxy for likely XBB-related sub-lineages, including XBB.1.5 that Dr. Scobie spoke of in her presentation. Testing and analysis were completed between December 1st, 2022, and January 13th, 2023, and these results were published yesterday in CDC's Morbidity and Mortality Weekly Report. Next slide.

And here we see those results. And again, these were just published yesterday and are available on CDC's website for those looking for more in-depth data. On the left, I show age group and vaccine dose pattern, including the reference group, which received two, three, or four monovalent doses and no bivalent dose. An overall group, that's those who are two or more weeks out from their bivalent booster dose, and then a subset of that group, those zero to one month or two to three months since a bivalent booster dose. As mentioned on the previous slide, VE was calculated by S-gene target failure, or likely BA.5 related subline edges, shown here in blue, and S-gene target presence, or likely XBB-related sub-lineages, shown in pink.

Generally, VE against symptomatic infection is similar for the two sub-lineages and across age groups. Confidence intervals are wider for the XBB analysis due to fewer cases, and we're continuing to monitor this as XBB.1.5 continues to increase nationally. Additionally, we've not seen substantial evidence of waning so far, but only had stable estimates through three months after receipt of the bivalent dose, due to case counts and timing of vaccine authorization, and so we'll continue to monitor potential waning throughout the spring. Next slide.

I'll now provide an update to an MMWR that was published by CDC in December, looking at the effectiveness of the bivalent booster vaccines against hospitalization in adults aged 65 years and up. The citation is shown here for those wanting more information on the original publication. Next slide.

The IVY network is a multi-state VE platform that uses a prospective test negative design. For this analysis participants were from 24 hospitals in 19 US states with hospitalizations between September 8th and December 29th, 2022. Note that this analysis includes one extra month of data beyond what was published in the MMWR in December. Participants are hospitalized with COVID-like illness and have a SARS-CoV-2 positive PCR or antigen test, and controls are negative for SARS-CoV-2 and influenza by real-time PCR. Next slide.

And here we have the updated IVY results with an extra month of data compared to the MMWR. On the left-hand side of the slide, you see the dosage pattern studied. I'll start first with a top section of the slide, which shows absolute VE. So that's VE comparing vaccinated people to unvaccinated people. The first estimate is for those who had a bivalent dose compared to those who had received no vaccine doses. And we see a VE for protection against hospitalization of 72%. Next, we show the VE of the two or more monovalent doses during the same time period and see that protection is 25% with a confidence interval crossing null. So these are individuals who received two or more monovalent doses but had not received a bivalent dose.

Moving to the bottom of the slide, we show relative VE, that is incremental or additional effectiveness of a bivalent dose compared to people who had two, three, or four monovalent doses. This is shown comparing people who got the bivalent dose to those who received only monovalent doses and is split by time since last monovalent dose. We see protection here of

between 61 and 65% with overlap in confidence intervals by time since last monovalent dose. Next slide.

I do want to note that the point estimates have changed somewhat since the MMWR was published. The published data, which included hospitalizations through November 30th, are shown on the left-hand part of the slide, and the updated data that I showed on the last slide with hospitalizations through December 29th are shown on the right-hand side. You can see that although point estimates have dropped somewhat, they remain within the confidence intervals of the original estimates and do not change overall conclusions that the bivalent vaccines are continuing to provide substantial protection against hospitalization compared to individuals with two, three, or four doses of monovalent vaccine only. Next slide. And next slide.

So to sup, from CDC vaccine effectiveness platforms, we found that the complete two dose monovalent Moderna primary series provided moderate protection at 57% against symptomatic infection for children aged three to five years in national pharmacy testing data. The partial two dose monovalent Pfizer series provided modest protection at 39% in children four to five years between doses two and three. And we did not have enough statistical power in this analysis to estimate VE for the complete three dose Pfizer primary series.

For adults, early estimates of the bivalent booster doses show that the vaccines provided added protection compared to earlier monovalent doses against symptomatic infection due to XBB and its sub-lineages, and protection appeared similar to that for BA.5 and its sub-lineages. Finally, updates to the VE of bivalent booster doses against hospitalization in adults confirm that the bivalent vaccines are providing protection against hospitalization compared to people who received two, three, or four doses of the monovalent vaccines and no bivalent dose. Those who had only received monovalent doses may have limited remaining protection. Next slide.

This presentation represents the work of dozens of individuals and teams at CDC and at various study sites, and I want to thank each of them for the countless hours they've put into generating high quality data and analysis for VRBPAC. Thank you, and I'll pass it on to the next presenter.

Dr. Perlman: Thank you, Dr. Link-Gelles. So before we have questions, we're going to have the other side of the CDC presentation, namely safety issues. And these are going to be presented by Dr. Shimabukuro and Dr. Klein. Dr. Shimabukuro is the Director of the Immunization Safety Office at the CDC, and Dr. Klein is the Director of the Kaiser Permanente Vaccine Study Center.

Dr. Shimabukuro: Thank you. Could you advance to the next slide? So, the objectives for today's presentation are describe CDC's Vaccine Safety Datalink Rapid Cycle Analysis monitoring methods and assessment processes for statistical signals, to describe VSD/RCA signal detection and signal assessment for ischemic stroke after the Pfizer bivalent booster dose, and to describe further evaluation and key next steps. Next slide.

So bivalent boosters first became available in the US in September 2022, and as of January 11th, there's been 49.5 million bivalent boosters administered in people five years and older. That includes 21.3 million doses in people 65 and older. CDC and partners monitor the safety of vaccines using multiple complimentary systems and the safety data continued to support CDC recommendations that everyone eligible for a COVID-19 mRNA bivalent booster get vaccinated. Next slide. And I'll turn it over to my colleague Dr. Klein.

Dr. Klein: Good morning. I'll be here to present the preliminary analyses of ischemic stroke after Pfizer bivalent booster doses. Next slide. So the Vaccine Safety Datalink, or VSD as you'll be hearing, for those of you who aren't familiar, was established in 1990. It's a collaborative

project between the CDC and nine integrated healthcare organizations and includes electronic health record data on approximately 12 and a half million individuals across all the sites. Next slide.

So in this slide, this shows the number of COVID-19 bivalent booster doses, and influenza boost vaccine doses administered over time amongst individuals over the age of 65 within the VSD. So focusing first on the red line, you can see those are the Pfizer bivalent boosters that you could see is much higher than the line in blue, which represents the Moderna bivalent boosters. Now, in green, you see how many more influenza vaccine doses were administered within the Vaccine Safety Datalink within this population. What's also striking is that you can see that how many, the timing of the vaccine that occurred mostly in September and by mid to late November, all the most, all the flu vaccine as well as the bivalent boosters had been administered within the Vaccine Safety Datalink, and that many more Pfizer bivalent doses were also administered than were Moderna in the VSD. Next slide.

So just to take a minute to talk about the VSD Rapid Cycle Analysis. So the strengths of ours that we include are our population, which is approximately again, 12 and a half million people, which is equal to approximately 4% of the US population across the VSD sites, which are geographically and racially and ethnically diverse. We use near real-time data with analyses updated weekly, and we have access to comprehensive medical records, including vaccinations and outcomes, which allowed rapid chart reviews to obtain additional clinical information as needed. Now these strengths have allowed us to use innovative methods for safety monitoring, including two that I'm just highlighting below because that's what I'll be talking about today. And those are the vaccinated current comparators. In this, we use recent vaccines as comparators, which is because we expect them to be more similar to current vaccinees than unvaccinated

individuals. And they offer the following advantages in that we can carefully adjust for potential biases associated with calendar time, which is very important, site and demographic factors, and analyses can begin sooner than alternative methods. Now in, in addition, we also do supplemental analyses, which we conduct on a weekly basis. And in these analyses, we use unvaccinated or unboosted as appropriate comparators, which we use to provide context for our primary analyses. And then, we believe that using vaccinated concurrent comparators with supplemental analyses offer substantial benefits when compared with either unvaccinated or historical comparators. Next slide.

So, for our rapid cycle analysis, or RCA, a for bivalent boosters, we use pre-specified outcomes, which we assessed during weekly sequential monitoring after COVID-19 bivalent booster. We looked at the risk of these outcomes 1 to 21 days following a bivalent vaccination compared with bivalent vaccinated individuals who are 22 to 42 days following the bivalent dose. And we use a signaling criteria for these analyses of a p-value less than 0.01, and that's a one-sided P-value. And I'll talk a little bit more about this in a minute. Next slide.

Turning to our analysis. So our analysis is a little bit complicated, so, I'll go through it here with the figure. So this shows vaccinee with outcome in the risk interval in the top panel. And this, that was represented by the heart. That's just a representation. It's not meant to mean anything specific. But for example, in the top panel, you could see that that person was vaccinated on September 30th with a bivalent booster. On October 3rd, that person had an outcome, which meant that they were in the 1-to-21-day risk interval post-vaccination. So on October 3rd, we take our comparators who are now in their comparison interval, 22 to 42 days post vaccination, because that person was vaccinated on September 3rd. So now on October 3rd, that person was in their comparison interval. So on each calendar day, that October 3rd, that an

outcome occurred in a vaccinee be compared to the vaccinees in their risk interval with similar vaccinations in their comparison. And by similar, for the comparators, we mean that on the same calendar day, they're the same age group, and at the same sex, race, ethnicity, and at the same VSD site. So what this means is that every analysis that we do are adjusted for age, sex, race, VSD site, and importantly, calendar day. Next slide.

So here's our case definition for our ischemic stroke definition that we've been using for the last two years or so for all of our RCA analyses. It's a complicated slide, but I will just focus in on the left hand side. Those are the ICD-10 codes that we use to find instant cases, and those included transient ischemic attacks as well as cerebral ischemic attacks and syndromes. On the right hand side, I do want to point out that we also excluded in all cases of individuals who had COVID-19 diagnosis or had COVID-19 positive tests in the 30 days prior to their stroke. I do want to point out that there is an error on this slide. It's not the first COVID diagnosis or test. It's actually any COVID within the last 30 days. So that is an error on the slide. Next slide.

So this is the bivalent RCA concurrent comparator analysis of ischemic strokes during the 1-to-21 day risk interval versus the 22-to-42 comparison interval. This represents the analysis I showed you the picture of, but what you can see here is that we, the analysis, are two groups, which we had pre-specified these two different age groups. And in the focusing on the 65 and over, you can see in red for the Pfizer, you look at the adjuster rate ratio at 1.47. You can see the confidence intervals, which do not include one, but more importantly, but actually is our criteria is our one-sided P value. In red, you can see a 0.005, and that did meet the signaling criteria of less than 0.01. Whereas, we did not see that — none of the other age groups or other boosts, Moderna boosters, have not signaled. Not. Next slide.

So just to take a minute of what happens when we have a signal, and I should point out that that was from January 8th, that data I just showed you, but that we had actually been signaling for several weeks at that point. So what happens when we have an RCA signal within VSD and to assess it, whether reflects a real effective vaccination on an outcome. And I will just mention that over the nearly 20 years that VSD has been doing RCA, we have had several signals — actually, it's not that uncommon to have a signal on which we do an assessment to find out whether it's a real effect or not. In this case, the steps that we take are to do data quality assessments for error anomalies or missing, late-arriving data. We do analyses using different comparators than the primary concurrent, in this case, for example, unboosted, unvaccinated, or historical comparators to supplement our primary analyses. We do additional investigation to provide context, which include background rates. We do graphic displays of outcome incidents day by day after vaccination, using temporal scan statistics to assess apparent clustering. And this exam is a temporal cluster of an outcome event in subgroups defined by demographic site or concomitant exposure, such as flu vaccine. If the signal is driven by strong association by one subgroup or VSD site, further analysis by site or subgroup are done as appropriate. We do chart reviews to confirm case and collect additional data, such as the date of symptom onset, and then we consider epidemiological studies to further investigate surveillance claims. So next slide.

So, here are the preliminary analyses of the ischemic scope after the bivalent booster amongst persons over the age of 65 years. Next slide. Next slide. This graph shows the ischemic stroke after Pfizer bivalent booster after age 65, counts and adjusted rate ratios. So what you see here are the number of cases and the, in the 1-to-21-day risk interval from October 16th all the way through January 8th. Next slide. Now what you see here, the cases, in the current, within the

comparison interval of 22-to-42-day interval. Again, through the same timeframe. I can see the next slide.

Now what you can see here is starting November 27th was the first time we saw a statistical signal for this outcome, for ischemic stroke. Now what you can see is this has been persistent, although attenuating over the last seven weeks. Next slide. And as of January 8th, where this data goes through, the rate ratio is 1.47. You can see the confidence intervals there that correspond to the table I showed you in an earlier slide. Couple things to point out here is that, although the number of cases in the risk interval in the blue have been increasing, but mostly increasing on a smaller — there have been more incremental increases, the number of cases in comparison have been increasing a little bit more over time, relatively speaking. And that is, as you can see here, the rate ratios have also been attenuating, and so now it's in the range of 1.5 percent for the last few weeks. Next slide.

So what this slide shows is when we first started seeing the signal, we started looking at the ischemic strokes by day after bivalent boosters. And this is amongst persons aged 65. So there's several things that are notable here on this graph. What you can see here is when we look for temporal clusterings, as I mentioned, we can see that there is a significant significantly significant cluster at days 11 to 12, excuse me, 11 to 22, with the P-value as you can see.

Some things to point out is for those of you familiar, familiar looking to these types of grafts, this is a cluster, but it's not quite so striking. You can see it, but it's not, it doesn't stand out as extremely striking. Unlike some other signals which we have seen, for example, myocarditis. It's an extremely strong signal that you can see without doing statistics. This one, perhaps, is more subtle, although present, and it is statistically significant. But the other thing that's important that I want you to keep in mind as you think about this graph is that when you look at

the comparison in a rule 22 to 42 days, it looks lower than the other parts of the graph. And so the question now becomes this, is this increased rate ratio? Is it because there's a higher rate within the risk interval, or is there unexpectedly lower rate during the comparison interval? And so I think perhaps it's a little of both, but we'll get, we'll talk about that more as we go on. Next slide.

So what we also did was we looked at some preliminary charts. Now this is a small subset of our cases, just to be clear, amongst those who are over the age 65, during days, only during days 11 to 21, post Pfizer bivalent booster vaccination. These were started early on after we first started the signal, and early December, we started looking at these charts. And so we viewed 24 cases and we found that 22 of the 24 were instant strokes, or TIAs, with a predictive value of 92%. So none had a history of stroke or TIAs. The median age of the cases was 77 and a half years. Symptom onset date rarely shifted from the electronic date. 5, or 23%, had a known history of SARS infection, but only one was in the last six months. Zero had any mention of recent exposure to SARS-CoV-2 in the chart notes. And 14, or 64%, had flu vaccine co-administered on the same day, and nearly all of those were high dose flu.

So for the outcomes, 13 of the 22 were discharged home. 4, or 18%, discharged home with home health. 2 of 22, or 9%, discharged to a skilled nursing facility and 3 died, or 14%. One of the deaths was in a 75- to 79-year-old male, approximately a month after the stroke, and death appeared likely to be related to the stroke. One stroke was in a 65- to 69-year-old female was noted after craniotomy, although the relationship with the surgery was unclear, and the death was due to cardiac arrest two and half months later. And then the third stroke, the third individual had a stroke at a 70-to 74-year-old male during a hospitalization for metastatic cancer. It was

subsequent death due to the cancer related complications during that same hospitalization. Next slide.

So we've also looked at, done some supplemental analyses. And in this one we looked at the ischemic strokes during the 1-to-21-day interval. In this case, these are the same cases as I showed you earlier in primary analysis, but now we're comparing them to unboosted, concurrent comparators. But those individuals are eligible for a bivalent booster in that they've had prior monovalent doses and they're concurrent comparators, which they're also well adjusted for age, sex, race, site, and calendar day. So these are adjusted analysis, but when we look at this analysis, we can see that, the adjusted rate ratio is 1.07, with a confidence interval which includes 1, and the p-value is not significant. So this is a little inconsistent with our findings from our signal primary analysis. So we're going back to the picture I showed you earlier with the graph where I mentioned about the comparators. We've done this additional supplemental analysis. Next slide.

And in this case what we've done is a little complicated, but it's now, this shows this ischemic strokes during the 1 to 21 and 22 to 42 day interval comparing the bivalent booster versus the unboosted concurrent comparators, again eligible for bivalent boosters. So in this slide, you can see the highlighted in red are those cases that occurred in our comparison interval, the 22 to 42 day interval. And when we compare those, again, with the unboosted boosted comparators, we can see a rate ratio which is significantly lower than 1, at 0.76. And you can see the P value. So what this is suggestive that perhaps, we are seeing a reduced rate of strokes in the comparison interval. Next slide.

So we've done some additional post-signal analyses, and in this one we've looked at concomitant high dose or adjuvanted flu vaccines. Next slide. So in this post signal analysis, they

were looking at, this is ischemic stroke instance during the days 1 to 21 day compared with days 22 to 42 day among 65-year-olds with and without simultaneous influenza vaccine. So when you look at the top row, you can see that those, those, that analysis represents individuals who receive both bivalent Pfizer and same-day, high-dose or adjuvanted flu vaccine. And you can see that there are 20 cases in the risk interval. Excuse me, 40 cases in the risk interval and 20 cases in the comparison are for an adjusted rate ratio of 2.

Now, just a word that adjusted rate ratio is not nearly as finally adjusted as our prior analysis. These analyses were only adjusted for age but not calendar time and other factors. You can see it's a significant rate ratio. However, when we look at the bivalent Pfizer without any same day flu, just by itself, we see 60 cases, 60 versus 58 in the comparison interval for adjusted rate ratio, just, 1.03 and not significant. So again, the rate this is, suggested that those who received concomitant vaccine had a higher rate ratio. However, back to what we talked about earlier, the question is, is that 40 higher than we would expect, given the increased stroke, or is it, is 20 less than we would expect in the comparison interval? So we've done some additional analysis in the next slide.

Again, it's a little complicated. I'll try to walk you through this. This one we looked at the expected cases after bivalent booster and high dose or adjuvanted flu vaccine based on ischemic stroke instance, and unboosted people eligible for booster. So we took those individuals, which I showed you in the earlier slide, who we use as the unboosted comparators. And we assessed how many cases of stroke we would expect in a three-week interval, which represents either a risk or comparison interval. We did it by age, in an age adjusted way, because stroke matters so much by age. And when you see as a total, you can see that in that period we would expect 34 and a half cases, in a three-week period, using that as a comparison. And what we observed, as I just

showed you in the earlier slide, we saw 40 cases in the risk interval. However, we only saw 20 in the comparison interval. So the 40 is a little bit more than we would expect, but the 20 is less than we would expect. So again, these findings are also suggestive that there's a reduced rate of stroke in the comparison interval. Next slide.

So, here's a summary of the findings of ischemic stroke following bivalent Pfizer COVID-19 mRNA booster vaccine. Again in persons aged 65 and older. So we have a statistical signal is persistent for seven weeks. I will say that in the data from just a couple days ago, it has attenuated substantially and actually it did not, has not signaled this past week for the first time. But it, the rate ratio had slowly attenuated from 1.92 to 1.47, but as continued to meet the same criteria until just a couple days ago. Additional signal investigation analysis. We found temporal clustering. Signal analysis found a significant cluster 11 to 22 days after vaccination. Supplemental analysis using unboosted concurrent comparative show a rate ratio of 1.07. That's not statistically significant. Of a small subset of charts reviewed, most confirmed cases had co-administered high dose or adjuvanted flu vaccine. Analyses evaluating concomitant high dose or adjuvanted flu vaccine showed a rate ratio of 2. That was statistically significant. Our separate analysis, which are not shown here, did not detect an elevated rate ratio for stroke after vaccine. Hold on. Those are separate data, not shown. And then finally — excuse me. Can you go back one more. Finally, supplemental analysis suggests comparison interval 22-to-42-day rates were lower than expected. Next slide.

So there are some additional considerations to think about with these data. So there are small numbers of strokes and imprecise rate ratios, which limit some analyses. We had reduced follow up time after Moderna reduced boosters due to distribution delays. And concomitant flu analyses were limited by small numbers. It's difficult to interpret the temporal clustering during

risk and comparison intervals. There's also possible unmeasured confounding. Results may have been influenced by confounders that vary over time. Importantly, do early adopters of five valent booster vaccines have a greater risk of near-term cardiovascular events? However, the same trend has not been observed for acute myocardial infarctions, and it's, it's difficult to, it's very challenging to attest the potential impacts of differential vaccine availability after the EUAs, so being there being so much more Pfizer than Moderna being available. And then, the possible roles of SARS-CoV-2 infection before the booster. So the background instance of effect of SARS-CoV-2 infection was rapidly changing during bivalent booster uptake.

And just a word, analysis that we did that which excluded the cases with the COVID-19 diagnosis or positive tests within the prior 30 days. So that was our case definition. However, asymptomatic infections and home antigen tests are not consistently documented in our EHR, which is not unique to VSD, but that is what's happened in the landscape of COVID. However, when we did chart reviews, we did not find recent SARS-CoV-2 infection exposure evidence. Next slide. I think I'll turn it back to Dr. Shimabukuro.

Dr. Shimabukuro: Thanks, Dr. Klein. Next slide please. So to sup. We'll continue to monitor weekly and explore potential data-related explanations for the statistical signal in VSD. We'll consider expanding chart reviews to all VSD sites, and we'll consult with other surveillance systems to better understand the possible role of concomitant high dose or adjuvanted flu vaccination with COVID-19 vaccination and the possible decreased rate of stroke in the three to six weeks following vaccination. Next slide.

Just want to reinforce that CDC continues to recommend that everyone eligible for a COVID-19 mRNA bivalent booster, or a flu vaccine get vaccinated. And CDC and FDA are engaged in epidemiologic analysis regarding co-administration of COVID-19 mRNA bivalent

booster and flu vaccines. Next slide. Next slide. And next slide. Thank you. That concludes our presentation, and we'll be happy to take questions.

Q & A

Dr. Perlman: Okay. Thank you, Dr. Shimabukuro and Dr. Klein, for very clear presentations. I think one comment before we take questions, I think as you know, it'll be very important to convey these data in a way that the public can understand the issue of ischemic strokes. So with that, we have about, oh, maybe six or seven minutes for questions. I see Dr. Ganz. Can you take it away?

Dr. Ganz: Thank you so much. I really appreciated the deep review of how these VSD, and these safety signals are looked at. And I appreciate this, ischemic stroke. My main question is just, I realize that you're looking at this potentially because this is the signal that you found more recently, but I'm wondering, and especially for the general public to discuss all of this, the other safety signals that are being monitored routinely, and what we can expect. And this'll be very relevant, specifically when we, if we're going to determine that these are going to be reviewed annually, or whenever the FDA meets. Because it's important to note that other safety parameters are being looked at, and I think it's important to note which ones they are, and that they get the same scrutiny. Thank you.

Dr. Shimabukuro: Could you please go to the very last slide of the, of the presentation and the extras? Because I think that will, it'll just give you some context for our monitoring. Is it possible to pull up the safety presentation and just go to the last slide?

Derek Bonner:This is Derek Bonner with AV support. Our technician is pulling that up for you.

Dr. Shimabukuro: Okay. That, that slide actually shows the, the very last slide in the entire presentation. So these are the VSD rapid cycle analysis, pre-specified surveillance outcomes, and the settings in which we're monitoring them. And I'll just reinforce, for the bivalent booster rapid cycle analysis, the only outcome we signaled for is ischemic stroke, for the Pfizer vaccine and the 65 and older. But here's a listing of our surveillance outcomes in VSD.

Dr. Gans: And are there any considerations, just to follow that up on the idea of long COVID, I'm looking at this list here, and obviously that's a, you know, group of symptoms, but how are we monitoring for that? Because there has been some, at least in the VAERS, some reporting.

Dr. Shimabukuro: So we, we are monitoring for, those types of, of symptoms. And, and VAERS, VAERS is basically a spontaneous reporting system. So any, anything can be reported in. That, that's a challenging outcome to monitor in, in, in VSD, I think it would probably be, multiple, sign and symptom, pods. So I, I would say that there, there are certain outcomes which, which lend themselves well to, to monitoring in VSD rapid cycle analysis. And I, I, maybe Dr. Klein can explain why certain outcomes, are, are, are, are, you know, are appropriate for RCA and then the problems with other outcomes which may have, you know, long-term insidious onset and, and, multiple symptomatology and, and a little more not, not really well-defined acute outcomes. Dr. Klein, if you want to take that on.

Dr. Klein: Certainly, but I think you've pretty much stated the type of outcomes that are really well suited for rapid cycle analysis, which we update dated weekly. We need to have clear diagnosis and, ones that we can identify readily. And the best outcomes that work best are ones

that occur relatively close proximity to vaccination and not, you know, perhaps weeks to months, but just more like days to weeks. And then that also we have a, a reasonable confidence that that represents, that the diagnosis represents the outcome. Because these are all done electronically. This is surveillance. And so, we want to, although as you can see here today, we do deep dives. We find signals. We want to have, we don't want to be constantly investigating signals if we don't have reasonable confidence in on our outcome to begin with. So something like long COVID, well, VSD could do a different type of study, but not a rapid cycle analysis. It's just not well given. Its long, insidious nature and it's indistinct diagnosis.

Dr. Perlman: Okay, thank you. I think we should go to the next question. Dr. Reingold.

Dr. Reingold: Thank you. So, I just want to ask a question or maybe just point to something, which is that when we think about the risks and benefits of vaccination, you know, if you think about influenza and influenza vaccination, my recollection is that studies show that people who have flu are at increased risk of stroke and heart attack for a protracted period of time after they recover. And so if the same were true for COVID-19, then I think you need to think about how much COVID you prevent, then how much of, perhaps the later strokes and heart attacks that might be associated with those COVID events, if, if there is an increased risk of stroke associated with vaccination. So to look at the overall benefits of vaccination we need to take that kind of effect into account as well. Thank you.

Dr. Shimabukuro: Thanks, Dr. Reingold. And I think that fairly shortly there will be an opportunity to present these findings in the context of benefit risk assessment at an ACIP meeting.

FDA Presentation

Dr. Perlman: Okay, thank you. I think we need to move on to the next presentation and we can come back to the other questions later. So the next presentation is by Dr. Forshee from the FDA, who's going to talk about, give us an update on the original COVID-19 vaccine and COVID-19 vaccine bivalent effectiveness and safety. So, Dr. Forshee is the Deputy Director of the Office of Biostatistics and Pharmacovigilance at the FDA.

Update on Original COVID-19 Vaccine and COVID-19 Vaccine Bivalent Effectiveness and Safety

Dr. Forshee: Good morning, everyone, and thanks for the opportunity to speak here today. Again, I'll be giving an update on some of our safety and effective analyses for the COVID-19 vaccines. Next slide, please.

This is an outline of the presentation. I'm going to start by giving a brief overview of the CBER Active Surveillance Program, which we call the Biologics Effectiveness and Safety, or BEST, Initiative. Then I'll talk about, our, safety surveillance for the bivalent COVID-19 mRNA vaccines. I'll provide an update on a study we did of real-world effectiveness of the mRNA COVID-19 vaccine among nursing home residents over 65 years of age. And then a conclusion for the presentation. Next slide, please.

This gives an overview of the data sources that we have available through our research partners in the BEST initiative. The point to make is that we have a wide variety of data sources

available. That includes claims, HER, and linked EHR and claims data sets that cover hundreds of millions of patients across a wide time range. Next slide, please.

For our current rapid cycle analysis, or sequential analysis, that I'll be discussing, we use the following data sources. We have data from the CMS Medicare system for ages 65+. This was approximately 36 million recipients that were included in that study. Three of the data partners were included in our sequential analyses. One point to note here is that we have a lot more individuals in the 65+ and 18-64 age ranges than we do in the pediatric population. Next slide, please.

One of the concerns that, all of us doing this sort of safety surveillance have had is that there has been some under reporting of the COVID-19 vaccinations. This was especially true early in the vaccine rollout, when many of the vaccines were given at NAS vaccination clinics, and those vaccinations were not always seen in the health claims databases. To help deal with that problem, we have worked very hard to establish agreements with many immunization information systems to supplement the information on COVID-19 vaccination status. Next slide, please.

I want to briefly remind the committee and the audience of the different phases of vaccine active surveillance. We generally begin with descriptive monitoring to provide descriptive statistics of the vaccine doses and selected adverse events. What I'll be focusing on in this presentation is the signal detection phase. In this phase, we typically perform sequential testing, so that we take repeated looks as vaccine doses accumulate. And the goal here is to identify potential safety risks early, so that we can provide further investigation. It's important to note that at this stage, the signal detection methods do not, prove any causal relationship. They only tell us where we may want to look more to better understand what we have found. The final

stage, which we are not at yet in our study is the signal evaluation stage, which uses more robust study designs to evaluate potential safety signals seen in the signal detection phase or raised from other sources. Next slide please.

Now I'm going to move to talk about the status of our bivalent COVID-19 mRNA vaccine safety surveillance Next slide, please.

So this summarizes, the administered doses that we have observed by age group so far in our rapid cycle analysis. For the 65 plus population, and again, this is our Medicare population, we've observed more than 7.3 million bivalent COVID-19 vaccine administrations. The majority of those have been for the Pfizer BNT vaccine, with more than 4.2 million doses for that. The numbers for the younger age groups are smaller, and we only have 210,000 bivalent vaccines observed so far in the youngest age group. Next slide, please.

Just briefly, I wanted to discuss the study design that we're using here. Again, this is a rapid cycle analysis that cannot establish a causal association. We look at a number of age populations. the exposures that we're looking at are the two bivalent mRNA COVID-19 vaccines. We're using a method called, MaxSPRT. That stands for Sequential Probability Ratio Test. And the comparator that we are using is our historical rates. Next slide.

This is a list of the outcomes that we are monitoring. They are similar to the outcomes that CDC monitors. And we've had numerous discussions about the adverse events that we're each monitoring. The closest analogue to the ischemic stroke that was discussed in the previous presentation in our analysis is non-hemorrhagic stroke. The key difference between the two is that we did not include transient ischemic attacks, or TIA, in our definition of non-hemorrhagic stroke. Next slide.

So this shows the signals that have been detected so far in our sequential analysis of the bivalent vaccines. Looking first at the Medicare population ages 65 years and older. We have so far not detected any signals, including for non-hemorrhagic stroke. And I should note that non-hemorrhagic stroke has reached the predefined limit of the safety surveillance because of the number of outcomes that we have observed. In the adult population, the only signal that we have seen so far has been a signal for myocarditis/pericarditis for the Pfizer BNT bivalent vaccine. This was in the 18- to 35-year-old population. This is something that was observed with the monovalent versions of the vaccine as well. Next slide.

Several of our outcomes have already completed the surveillance period without a signal. And therefore they will not signal during this analysis. They include acute myocardial infarction, deep vein thrombosis, Bell's palsy and common side thrombosis with thrombocytopenia. Those are for the Pfizer vaccine only. Non-hemorrhagic stroke has completed the surveillance period for both vaccines, and the surveillance period has ended for pulmonary embolism for the Pfizer vaccine. Next slide.

This provides a little more detail on the rate ratios that we saw for the non-hemorrhagic stroke for the Pfizer bivalent. Again, we were comparing to 2019 historic rates. The key point that I want to note here is that the rates of non-hemorrhagic stroke that we have seen in our surveillance are below the levels that we see in our historical rate comparison. In the most recent observation period, the rate ratio was 0.76. And again, we've reached the maximlength of surveillance without a signal. Next slide.

The issue of concomitant influenza vaccination, especially with high dose or adjuvanted vaccines, was highlighted during Dr. Klein's presentation. In our analysis we've seen approximately 4.25 million doses of the Pfizer BioNTech bivalent vaccine in individual 65 years

and older. Of those, 38% of the recipients who received a Pfizer bivalent COVID-19 booster also received a seasonal influenza vaccination on the same day. And the vast majority of these were either high dose or adjuvanted vaccines. In addition, 78% received a seasonal influenza of vaccine, vaccination, within plus or minus 42 days from the receipt of their COVID-19 bivalent booster. We're continuing to do more work to segment out the different influenza vaccines administered. And again, no signal at this time has been seen for hemorrhagic stroke, even though we have 38% that received a concomitant influenza vaccine or vaccination. Next slide.

So in summary, these are the results of a large-scale signal detection study of the two COVID-19 mRNA bivalent vaccines. It's been conducted in multiple databases and is still ongoing for some age ranges and some outcomes. The only signal we have detected so far is for myocarditis/pericarditis following the Pfizer bivalent vaccine among adults 18 to 35 years old. For the adults 65 years and older, several adverse events have already completed the surveillance period because of the large number of doses and outcomes that we have seen. As I've mentioned before, these signal detection studies do not establish a causal relationship, and further evaluation of signals is required using more robust study designs. The surveillance is ongoing, and particularly in the younger age groups, and will be expanded to the youngest, less than five-year-old recipients as we get sufficient exposure in that group. Next slide.

Because of the results that have been presented from the CDC and VSD analyses, we have done further exploration as to into other data sets, looking for information on the potential safety risk of ischemic stroke. So far, the data that we have seen suggests the absence of a safety risk for the bivalent boosters in age 65 years and older. There have been no excess reports of stroke from VAERS. I've just reported on what we found in our CMS sequential analysis showing no increased risk in stroke. The Veteran's Affairs database has also done a preliminary

run that did not find an increase in stroke. We contacted a number of our international regulatory agencies, and various countries in Europe, as well as Israel, have indicated no increased risk of stroke in their surveillance systems.

We also contacted Pfizer and they consulted their global safety database, and they did not see any increase or a signal for the for ischemic stroke in their systems. In any case, because of the information that we have seen, we at FDA have launched a formal epidemiological study. We're working on the protocol right now to study in particular the concomitant administration of high dose or adjuvanted influenza vaccines and the COVID-19 bivalent vaccine in order to prepare for potential vaccine co-administration in the 2023/2024 SEASON. Next slide.

Next, I'm going to discuss data that we have on real-world effectiveness of the mRNA COVID-19 vaccines among US nursing home residents age 65 years and older. This will be for the monovalent boosters because we have not accumulated sufficient data on the bivalent to estimate the real-world effectiveness yet. Next slide. Next slide.

For background, we all know that the COVID-19 pandemic caused substantial morbidity and mortality, especially among older adults residing in nursing homes. Therefore, we designed a study specifically looking at nursing home residents to understand the effectiveness of the mRNA COVID-19 vaccines among this population and across time in order to support effective policymaking and vaccine development. Next slide.

The observation period for the study was December 13th, 2020, through November 20th, 2021. The exposures looked at mRNA COVID-19 vaccination status. The population that we were looking at was the Medicare Fee-for-Service beneficiaries aged greater than or equal to 65

years residing in US nursing homes. And the primary outcome was COVID-19 related deaths, COVID-19 hospitalizations, and combined COVID-19 hospitalization or death. Next slide.

As was mentioned before, we are always concerned about potential under-reporting in vaccination and the bias that that might introduce. To minimize that in this study, we conducted a quantitative bias analysis during the protocol development stage to evaluate the impact of potential exposure misclassification. And we also used exclusion criteria, and we excluded beneficiaries who resided in a nursing home that reported less than 10% of residents were vaccinated on or before March 1st, 2021, or if a second or third dose was observed without the preceding dose. Next slide, please.

These are the FDA final study populations. There were a total of approximately 348,000 nursing home residents aged 65 years are older. The majority of those 61% were in the two-dose cohort and 21% were in the booster cohort. Next slide.

This chart summarizes the adjusted vaccine effectiveness for COVID-19 associated death in the pre-Delta and Delta periods during periods of high circulation of COVID-19. So you can see that in the pre-Delta period, where there was 0% delta circulation, the two-dose vaccination was providing almost a 70% effectiveness against COVID-19 associated death. When we moved forward to the period where Delta was the predominant circulating strain, those who had only received two doses had seen their effectiveness fall to 55.7%, whereas those who had received a booster saw their vaccine effectiveness of 88.7%. Next slide, please.

This slide is a similar slide looking at COVID-19 associated hospitalization. This is for all time periods. The statistical method we were using did not detect any interaction between vaccine effectiveness and the circulation, level of circulation. So we see a similar pattern here of

65.3% of vaccine effectiveness for two doses in the pre-Delta period. During the Delta period, those with only two doses saw the vaccine effectiveness fall to 40.4%, whereas those who received a booster saw 76.8% vaccine effectiveness. Next slide, please.

There are a couple of limitations to our study in particular. It's impossible for us to disentangle the possible effect of the waning of immunity in the time since someone received their vaccinations from the change in the circulating strains with the rise of Delta during the time period that we are we were looking at. Both of these likely contributed to the observed decrease in effectiveness in the higher Delta periods. And also the study period does not extend far enough into the booster dose administration phase for us to make estimates for the vaccine effectiveness of the bivalent booster doses. Next slide.

So concluding the presentation, the best initiative leverages its infrastructure and capacity to generate data for evidence-based regulatory decisions. We try to rapidly respond to emerging public health concerns. We use our resources to expand the scientific evidence database and to inform and promote public health. Next slide.

This is a large team effort and I'm presenting on behalf of the team. Next slide, please. I think that may be the end of the presentation. So thank you very much for your time and attention.

Q & A

Dr. Perlman: Thank you for a very good presentation. We have about 10 minutes for questions, so Dr. Chatterjee?

Dr. Chatterjee:Yes. Thank you very much Dr. Perlman. Dr. Forshee, thank you for your presentation. I have two questions for you. The first one is with regard to the definition of ischemic versus hemorrhagic stroke, because it seemed like for the VSD analysis, they used ischemic stroke and for the FDA's analysis, non-hemorrhagic stroke was, was used. Is there a material difference between those two definitions?

Dr. Forshee: The key difference between the two is that the CDC definition included transient ischemic attacks as part of their definition of ischemic stroke, whereas we did not include TIA as part of our definition of non-hemorrhagic stroke.

Dr. Chatterjee:Thank you. The second question is with regard to this study that the FDA's planning. With the signal that emerged from the VSD Rapid Cycle analysis, I am wondering if it would be prudent to separate the doses, flu vaccine and COVID vaccines, for those over 65 years of age. And I'd just like to learn a little bit more about this study that's planned. What, how is the FDA going to conduct this study?

Dr. Forshee: Yes, so we are planning to conduct a self-controlled analysis using risk windows and control windows after COVID-19 vaccination. We are going to specifically address the question of concomitant influenza vaccinations by looking at individuals who received either an adjuvanted or high dose influenza vaccine on the same day that they received their COVID-19 bivalent booster. So we will have that as one of the analyses in the study to assess whether there is this interaction effect between receiving an adjuvanted or high dose influenza vaccine at the same time as your bivalent vaccine. I'm

Dr. Forshee: I’m sorry, could I ask a follow up question, Dr. Forshee?

Dr. Forshee: Of course.

Dr. Perlman: Yes.

Dr. Chatterjee:Yes. So I'm, I'm still unclear about whether this study is sort of a passive analysis of whatever people receive versus obtaining informed consent for those who receive both vaccines on the same day, and those that are separated.

Dr. Forshee: This is going to be a study using health claims data in the Medicare system. And so while it is, is active surveillance, we are not going to be doing any intervention for this study.

Dr. Chatterjee:Thank you.

Dr. Reingold: Okay. Thank you. Dr. Reingold?

Dr. Reingold: Yeah. Hi. So this goes back to something Dr. Meissner asked about a little earlier, in the concern that people who have a positive SARS-CoV-2 test might not actually have COVID-19, but have some incidental illness, but happen to have a positive test because everybody's getting tested on admission to the hospital. So, while I grant that that could potentially lead to an overestimate of the burden of COVID-19, am I correct that in your studies and in the studies of by CDC, Dr. Ruth Gelles and others that if there is a misclassification of the outcome, that is, if we're including the individuals who don't really have Covid, but have some other illness and just happen to have a positive test, that that would lead you to underestimate the vaccine effectiveness against Covid itself?

Dr. Forshee: Yes, I believe that is correct.

Dr. Reingold: Thank you.

Dr. Perlman: Okay. Thank you. Dr. McInnes?

Dr. McInnes: Thank you. I'm going to make a plea for consistency of language usage. So for those of us who worked in both bacterial and viral vaccines, co-administration has a different context. So co-administration can be pulling up two vaccines into the same syringe, and that is not the same as concomitant administration of vaccines. And I would make a plea for harmonization of language between the agencies. It makes it much easier to understand these already very difficult data. So thank you.

Dr. Forshee: Thank you very much for that point. We will keep that in mind for future communications.

Dr. Perlman: Thank you. Dr. Nelson?

Dr. Nelson: Thank you, Dr. Forshee, for a fantastic presentation. Now, I'm going to agree with Dr. Gans, who stated with the last presentation, it's important to report negative findings with respect to signals. And in particular, I noted Dr. Forshee, from your study, you identified a myo/pericarditis signal with Pfizer for the 18 to 35 group. My question is, and I understand the limitations of the methodology of how this data was generated, but how is that data consumed and compared with the results of other studies within the FDA? Is there a mechanism to reconcile or share cases, or are there privacy concerns that prevent the deep dive that might get at whether or not there is an important signal for this issue, which is very public with respect to concern and vaccine hesitancy in this younger age group?

Dr. Forshee: Yes, we do conduct follow up studies for any signal that is detected, beginning first with requesting medical records to evaluate the likelihood that the, in this case myocarditis/pericarditis cases, are associated with the vaccine. This association has been seen with the mRNA COVID-19 vaccines, with the monovalent vaccines, and in other systems. So

that has been considered during all of our decisions about authorizations or approvals for vaccines. We have carefully looked at the benefit risk assessment for myocarditis/pericarditis in our considerations of authorizations and approvals, and some of those studies have already been published.

Dr. Nelson: Thank you.

Dr. Perlman: Okay. thank you. And I think we have no more questions, so we can move on to the next topic. Thank you, Dr. Forshee.

Dr. Forshee: Thank you.

NIH Presentation

Dr. Perlman: The next topic is from Dr. Beigel, who's the associate director for clinical research at the NIH NIAID, and he's going to talk about evaluation of improved COVID-19 vaccines.

Evaluation of Improved Generation COVID-19 Vaccines

Dr. Beigel: Good morning. So thank you for inviting me to talk. So this is a slightly different topic than what you've heard so far, but I was asked to talk about how we would think about evaluation of NextGen vaccines. This slide is my disclosures. I don't plan on talking. I've got no personal or financial relationships, but I think it's important to just make sure everything gets disclosed.

So the prior conversations, presentations, set up the need for the variants, understanding the variants over time, the emergence of new variants, what happens to that, the decisions behind the prototype vaccine. So to help frame how we are thinking about this and why we think that we need the NextGen vaccines, it's helpful to understand our current strategies. So our current strategy is to use antigenically diverse vaccine strains. So in March of 2022, we started a study called the CoVAIL Study, and I actually came to VRBPAC in April, I think, to talk about our thoughts on this. But it is a study where we look at using the current available vaccines. And in this case, we looked, we worked closely with Moderna, Pfizer and, and Sanofi. And we say, what are the different antigens that we could use and how do we kind of broaden that immune response? And is there a way to use antigenically diverse strains, run that immune response for better protection against variants.

So we started the study. It's adults only, and everybody coming in has already had their primary series. They already had a booster. Could be homologous or heterologous. It can, it includes infected, previously infected, and previously non-infected or not known infected. And then they were enrolled, and they were enrolled by stage. And if you look on the right, those are the different stages. So when they came in, they were enrolled by stage and then randomized to one of these different constructs. So comparisons within a stage, I think, are valid, because that's completely randomized comparisons across stage. It's a different population, it's a different time. So we try not to do comparisons across stage.

So, just kind of walking through the Moderna. Everything is compared to prototype. But then we looked at Beta-Omicron, Delta-Omicron, Omicron alone, Omicron prototype. This was March. So we had the BA.1 product available, not the 4/5. For Pfizer, same thing. I mean, we compared to wild type, but we also looked at Beta-Omicron, Omicron alone, Beta alone. And

same for Sanofi. They didn't have an Omicron at the time, so we looked at prototype Beta or the bivalent. We look at that data and think about things in terms of the analysis.

We think about things in terms of antigenic maps. So I, in the VRBPAC in April, I discussed the antigenic maps. Just to kind of give, I think most people on the VRBPAC are familiar with, but to give a refresher, all it does, it's a visualization tool. It's not the analysis. It's not a lab test. It's just a visualization tool, but it helps you understand relative distance of the antigens and how these are related to each other. So on that map, on the left side D614G is this dot in blue. Any distance in any direction is a twofold dilution. And they take different populations, people that were given the mRNA-1273, people that had Beta infection, people that had Omicron infection. You take different populations. You understand the immune response in that population. And then you start triangulating this, and then you get some understanding of how these different antigens are related to each other. All that shows is relative distance. It doesn't tell you absolute values of anything.

So on top of that map, we use antibody landscapes, and that's what's on the right, where you actually start seeing titers and you start seeing titers and how they vary across that map. So you take that map, just kind of flatten it out. The D614G is this peak here. The Omicron is this red dot here. That map just flattened out. And this is an example of the mRNA-1273 sera. And you see the peak over the D614G, and then this slope drifting down lower and lower titers as you get towards these antigenically more contemporaneous strains, like Omicron and BA.1.

So this is the CoVAIL, the data. So first, let me just go through the setup. This is the Moderna set. So all those arms that we talked about, this is day one at the bottom. This is day 614G. This is the map trying to just simplify to the dots. B.1, BA.4/5 is here. So what you see is not unexpected. At baseline, again, after two vaccines and then a booster, at baseline they've got

moderate titers, but then they drift down considerably as you get towards BA.1, BA.4/5 post-boost. And this is 91 days post-boost. We increase that. Everything, regardless of whether it's prototype or any of the variants we use, you increase those titers, you increase that across that antigenic space, you flatten that out. So regardless of what we use, we accomplish that.

This red slope here is prototype. Everything else, those other four arms, are all right on top of each other. And so, what you start seeing is, yes, they all work. Prototype increases, prototype increases titers across that map, but anything besides prototype does it slightly better. And this is Delta Omicron, Prototype Omicron, Omicron alone, they all really look remarkably similar, but different than prototype.

Pfizer, it's a really similar story. Again, the day 1 at the bottom, the day 91 at the top. What everything, regardless of what we use well, increases that curve, increases that antibody response, across those different variants. But everything is better than prototype alone. And even things that didn't contain Omicron are better to Omicron. Like Beta. I mean, Beta's at the top here, Beta's this yellow near the top. So that increases, that new antigen increases response to Omicron.

This is Sanofi. I mean, again, a really similar story. The day 1, the day 91, you flatten it. You increase the titers. You flatten it across that antigenic space. But Beta and prototype Beta, better than prototype alone. It's important to, the last point is that bivalent vaccines perform similar, you know, Beta alone, you don't need the, the prototype Beta alone performs similar to monovalent vaccines.

This is a smaller data set. This is done in a different lab because it can get us more contemporaneous strains quicker. So this is the one of the arms from Moderna, the Moderna

Omicron BA.1 and prototype arm. And what I want to point out here is just how fast we're, how well we keep up with newly emerging variants. So we started the study in, in March, April, this part of the study in March, April. BA.1 titers, good. I mean, do you see where we're at? Come in, titers around a hundred. We boosted titers well over several thousand and kind of drift down by day 91. But as we get more antigenically contemporaneous, and you see the BA.4/5 here.

You don't get that same response. You see the BQ.1 and the XBB here. Here, I don't have a day zero, but, peaks, I mean, peak response to XBBB is right around a hundred. And that's that blue dotted line. So, variants that emerge within nine months are titers, are relatively low to those new variants. And why did I highlight that line of a hundred? Well, I think there's data to suggest, correlative protection analysis, that efficacy decreases as lower neutralizing antibody titers. And this is a paper from Gilbert, but you just see this consistent message of correlation of, of protection, decreasing titers. And once you get down to a hundred, you start seeing that efficacy get below 90.

So I want to highlight that the antibodies are good, sorry, the vaccines are good against severe disease and actually are the best against severe disease. There is data about asymptomatic disease, and there's cohort studies that suggest protection for asymptomatic disease. And I highlighted one. There's several of these. But it does work for asymptomatic disease. But the efficacy against asymptomatic is lower than symptomatic disease. And at the bottom, if you look at VE for severe hospitalization, severe Covid cases, symptomatic Covid, or asymptomatic, you move from a VE of 97, to 93, to 63. So the current vaccines are really good for severe okay or good for symptomatic, but as you start getting asymptomatic disease, it gets down towards the sixties.

What do we know about transmission? A slightly different concept. Again, there are cohort studies suggest protection against transmission, and there are protections within a household. And if a person is infected, you get similar peak titers and, and maybe slightly less duration of shedding. That might decrease the transmission some. But a complete protection against transmission is lacking. I'll be the first to admit, I mean, definitive studies of awaiting transmission, transmissibility, are lacking. I mean, there are small data sets, but the data suggest some transmission, some protection against transmission. But it's modest at best.

So just to reiterate, the current vaccines remain effective against COVID-19. The efficacy against severe disease, and that's obviously the most important outcome, symptomatic disease, is a little less. And asymptomatic disease and transmission is, seems less than that. We've shown high titers aren't sustained over long periods of time. And the cross-reactive antibodies to new variants that emerge within a year are marginal. I.e., we weren't successful in flattening that landscape that I showed you, that antibody landscape, we weren't successful in flattening it enough to cover newly emerging variants with high titers.

So that brings us to why we think, you know, we need next generation SARS-CoV-2 vaccines. And when we think about it, the key properties are one or more of these: enhanced breadth of protection and this, this concept of variant proof, I think different groups define that differently, improved durability, or enhanced ability to block infection and transmission. And how would you go about that? I think there's a number of groups working on this. There's a new antigen and constructs to generate broader immune response. Some are going after conserved elements, some are going after more of a mosaic approach. There there's different vaccines that might give different, more durable immune response. And then, there are groups targeting mucosal immunity and intranasal or oral administration to generate a mucosal immune response.

And there's some groups doing a parenteral administration, but with something that will give you more mucosal immunity.

So how do we advance this field? So for Operation Warp Speed, there was good data to support which vaccines to advance. There was decades of preclinical work supporting the antibody role in minimizing severe disease. There was work with the mRNA vaccine platforms there and the other platforms. So, we knew which ones to advance. For NextGen vaccines, especially mucosal, I'm going to argue that more data is needed. Which vaccines are likely to increase the breath and protection and durability is not clear. How do you define the vaccines or how do you, how do you pick the vaccines that will limit asymptomatic transmission, asymptomatic infection and transmission. And what are the immune correlates associated with that protection of asymptomatic infection and transmission. We know it's not all antibody. So this is an analysis, again from Peter Gilbert, that showed how much of the VE can be attributed to antibody titers, in the analysis they call that inactive VE, and how much are, is through other mechanisms, other pathways, and that's direct VE. And then that proportion is on the far-right side. And that proportion in this paper, this is the Moderna paper, suggested 68% of VE is attributed to antibody.

But then I bring in this table that I've already showed you about different VEs for protection against severe or symptomatic, or asymptomatic. And the role of neutralizing antibody that I just said, that 68% mediated, is likely not true and is not going to be equal across these different outcomes. And how do we start understanding what forex us against severe, what protects us against severe, what protects us against asymptomatic, et cetera. So in addition to neutralizing antibodies, what mediators might be contributing?

This is a paper that we've done that we published a year ago. That was, we call it the mix and match study. But it is looking at different primary series, different boosts. So this is people coming in with the Ad26, the mRNA-1273 or the Pfizer, and boosted with different things, boosted with mRNA, boosted with Ad26, et cetera. This is the cell mediated immunity from that. And you see that there are differences. I mean, the mRNA, both Pfizer and Moderna had a very different CD4 response than the Ad26. but the, the Ad26 has a very different CD8 response. So coming back to that prior, if we know antibodies aren't everything and we know cell-mediated immunities might be a role here, and how do we start differentiating cell-mediated immunity for severe versus asymptomatic disease?

So there are analyses ongoing for this. I mean, from our COVAIL trial, we're working with Peter Gilbert again on that. And they're looking at neutralizing antibodies and T-cell analysis. And we've got T-cells on about 70% of that group. So that analysis is ongoing. Some companies are, there are pivotal studies that also had some cells. And Janssen, the COV2008 study has some cell-mediated immunity, and there's probably other groups that I'm didn't mention, but the point that there are groups working on cell media immunity. But there might be other things. We know that nasal IgA titers are related to protection. This is a paper that just showed nasal IgA or IgG, IgA is that darker blue and IgG is the lighter blue. And the risk of Omicron breakthrough related to those. And the higher the IgA, the better. And that's what this analysis shows.

But that's baseline IgA titers. That doesn't tell me how I modify that. That doesn't tell me if a vaccine changes that, and that doesn't tell me if changes that I measure are actually going to be related to differences in vaccine efficacy. Especially those outcomes of transmission and asymptomatic infection that we are increasingly interested about. So, you know, it's really hard

to kind of clarify what to measure from mucosal — I don't know what happened there — what to measure from mucosal vaccines. The contributions from systemic or mucosal. The mucosal antibodies, is that what I'm interested in? Or a mucosal cell resident immune response? Do I look in the nose or the mouth? The nasal or salivary? IgA or IgG? And if I'm looking at cells, or, I think CD4 or CD8? And you start seeing the complexity and the gaps where we need a lot more information to really understand what to measure from mucosal vaccines.

So coming back to kind of frame the question that I was asked, I mean if, how do you evaluate next generation Covid vaccines? So the evaluation of current generation Covid vaccines, either efficacy trial for prevention of symptomatic disease, and or non-inferior immunogenicity. And I think there have been attempts to try to outline what that would look like. So the, the evaluation of the NextGen vaccine, I think, starts at the same place. Either pivotal trials for efficacy, non-inferior immunogenicity, and there's going to be some vaccines that just come in and say, we've got better breadth, we've got better durability. And that will be a huge improvement for us to get there.

But then there's going to be others to really say, in addition to those, how do we measure outcomes that we're now interested in? And that includes asymptomatic disease, that includes transmission. And to really get there, to advance those vaccines with these additional outcomes, we need to understand and identify the immune markers related to the outcomes of interest. Think about and try to analyze the immune response necessary to impact transmission or asymptomatic and/or asymptomatic infection. Evaluate the correlates of production using those parameters. So again, just because an immune marker is there doesn't tell me if it if it is correlated with parameters with the protection. Standardized sampling technique. And develop optimized and validated assays. And I think all these right now are lacking in this field.

So to wrap it up, I tried to make a case that there's a public health need for next generation vaccines. Some next generation vaccines will be advanced using data and assays similar to the pivotal trials of our current vaccines. Broader protection against emerging variants, and we can discuss what that looks like. Increased durability. But we also need to understand the immune responses that are protecting against infection and asymptomatic infection, transmission. And these are the outcomes that are increasingly important to us, because we've accomplished that first task of preventing the severe outcomes, minimizing the symptomatic disease. Now let's talk about how we get to this next step. And I think, together, this set of data will let us identify the most promising vaccine candidates for to further decrease COVID-19 disease. So with that, I'll stop, and we'll take questions.

Q & A

Dr. Perlman: Dr. Thanks, Dr. Beigel for an excellent presentation. We have five minutes for questions. So, Dr. Ganz?

Dr. Gans: Thank you so much. I mean it was beautiful presentation. I think you really outlined some of the challenges that many of us on this committee have been really also speaking about for quite some time, particularly the correlates of immunity. And you outlined them beautifully. I mean, my concern is time. And we're always at this point of having to make decisions without that data that you suggest. So I just wanted to really applaud the conversation now. I mean, but to push people to really look at these markers.

I did have a question about the data that you actually presented and that then tipped you into this, of course we need vaccines that look at different mechanisms. And that was that, I think the data that you presented actually didn't include any of the bivalents with the B.4/B.5, if I'm correct. In looking at that. It went by very quickly and really only had the B.1. And we know, again, according to your graph, that there actually is more characteristics that are related to the B.4/5 in the… so anyway, I just wanted to say that there could have been some better variant control

Dr. Beigel: Without a doubt. And just to bring it back, at the very bottom, and I didn't highlight it, we started in March. And at the time we had the BA.1. So that was how we constructed the trial. We did add a stage four, which is wildtype BA.1 versus wildtype BA.4/5. We're just starting to get that data. And the end that we had was really small. So, we chose actually not to present that, because I think that's way too speculative at this juncture.

Dr. Perlman: Okay. Thank you. Dr. Levy?

Dr. Levy: Yeah. thank you, Dr. Beigel, for an excellent presentation. Really a critical topic I've brought up at many of these meetings. As you may know, you know, the desire of myself and I know other committee members to have a better sense of how these vaccines are protecting. We need to learn as a community how to keep doing it better. You know, the enormous success and progress, and yet a long way to go as you highlight regarding the antibodies. As we know, these are all correlations we're measuring. We don't really prove the mechanism of vaccine efficacy. And there could be deeper ways, of course, to measure the antibody system. Serology and other approaches that give deeper insight into the types, exact types, of antibody that are being induced. The T-cells, you mentioned CD4, CD8. We don't talk a lot here about innate immunity. Not that that's probably the main mechanism, but there could be

aspects. It's already been shown that mRNA vaccines can reprogram innate immunity and change innate immune parameters in humans. And maybe those contribute to early protection possibly.

And then of course, how do these correlates of protection play out in different populations? They might not be identical. Their contribution in very young infants versus older adults versus those with comorbidities versus immunocompromised. Systems biology can be a tool to cast a broad net, you know, without any bias as to which mechanisms may most contribute, but it's costly. And how do you nest that into the clinical studies? So, you know, you raise a whole range of very, very important concepts and principles, and I hope FDA will continue to reflect on how to best take this information forward and encourage or require sponsors to gather more information in a standardized way across these different arms of the human immune system so we keep learning and keep doing this better. And I look forward to continuing that conversation. We'll also be in touch offline. Thank you.

Dr. Perlman: Thank you. Dr. Rubin.

Dr. Rubin: Thanks, Dr. Beigel. I'll join everyone else in thanking you. I guess the question is, if you induce immunity using a completely different mechanism, do you expect that the correlates of immunity are going to be the same?

Dr. Beigel: I mean, you're absolutely right. The answer's no. I mean, that was what you were implying, but you're absolutely right with that suggestion. I think if you're inducing a different mechanism, like a mucosal, you might, you really have to do the evaluation to say what is the breakthrough and start getting that information of what the correlates are. Because we can measure things, but I don't know what they're going to mean, right? We're going to measure IgA,

but I'm not sure what that, and the mucosal, but I don't know what that necessarily means until you start doing correlates of protection analysis. And there's no reason to believe that the correlates of protection across the different platforms will be the same. You're absolutely right.

Dr. Perlman: Okay. Thank you. Dr. Hildreth, a brief question?

Dr. Hildreth: Thank you, Dr. Perlman. And thank you, Dr. Beigel. I have a question about convergent evolution. More than 9 million viruses have been sequenced, and it's very clear that there's a convergent evolution happening, especially in the receptor binding domain of the spike protein. Are any of the vaccine approaches you're taking, taking into consideration the? This push might help us a lot if we could somehow factor that into our design of vaccines.

Dr. Beigel: Yeah. I mean, it's an interesting question. I don't think we're to a point where we can actually predict the vaccines very well. All right? We are to a point where we know what that epigenetic map looks like in the, where, how the different variants are there. We can get to a point where, and groups are working on this, where you see genetic mutations and you start modeling and assessing the viral fitness. And so you kind of start nibbling around the edge of that map that we have. But I don't know what that entire map is. And until we're to a point where we can say, this is where we're at and this is the direction we're going, I, and we're not there. I mean, it would be great if we're there. We're just not there with this science.

Dr. Hildreth: Thank you so much.

Dr. Perlman: Thank you. So we have time now for a nine-minute break, coming back at 11:30 Eastern time, ‘cause we have a tight schedule until the public hearing at 1:30. So nine minutes, and we'll see everybody back here.

Moderna Presentation

Dr. Perlman: Okay, so welcome back from the break, and I think we can get started now with the Moderna presentation. So I want to introduce Dr. Lozito, who's going to start with the Moderna presentation. And we will have three presentations, each for about 30 minutes. So take it away, Dr. Lozito.

Introduction: Moderna COVID-19 Bivalent Vaccines Primary Series and Booster

Dr. Lozito: Good morning. My name is Antonella Lozito, Executive Director of Regulatory Affairs at Moderna. We'd like to thank the FDA and the VRBPAC for the opportunity to present new data supporting our COVID-19 bivalent vaccines, both as primary series and as a booster.

Since authorization, there have been more than 278 million doses of the bivalent vaccines distributed worldwide, and no new safety signals have been identified. Data from real-world studies show that our bivalent vaccines protect against infection and severe disease, including hospitalizations. Exploratory analyses from our large, randomized, active controlled trial provide additional information on COVID-19 incidence rates with the bivalent vaccine compared to the original vaccine. We've also seen consistent safety and immunogenicity with our bivalent vaccines against both the original strain and Omicron subvariants in animal and clinical trials. Importantly, data support the use of our Omicron containing bivalent vaccine as a primary series and booster in individuals six months of age and older. As part of our commitment to monitor

emerging variants of concern, we have observed cross-neutralization of the bivalent vaccines against emerging Omicron subvariants.

As we continue to monitor the changing variant landscape, we generate new preclinical and clinical data accordingly and develop new vaccines as directed by regulatory agencies. Our mRNA manufacturing capabilities allow us to rapidly respond to evolving public health needs. To that end, we support the FDA's recommendation for a globally harmonized decision-making process to update COVID-19 vaccine composition, similar to that which is used as regulatory basis for approval of influenza vaccines.

Here now is the agenda for the rest of our presentation. Thank you. I will now turn the presentation over to Dr. Das to present clinical and real-world data with Omicron-containing bivalent vaccines.

Clinical Data with Omicron-Containing mRNA-1273 Bivalent Vaccines

Dr. Das: Good morning. My name is Rita Das and I'm a Vice President of Clinical Development at Moderna. To date, more than 9,700 individuals have been vaccinated in clinical trials with a Moderna variant containing vaccine, and two Omicron-containing mRNA-1273 bivalent booster vaccines, the BA.4/5-containing vaccine and the BA.1-containing vaccine, are available worldwide. With the emergence of the SARS-CoV-2 variants. Early in the pandemic, we began generating data on adapting the sequences in the vaccine to better match circulating strains of the virus. We first did this in an open label study in adults, study 205, to enable rapid evaluation of immunogenicity and safety of the variant vaccines.

This slide shows the weekly new cases of SARS-CoV-2, according to time and variant predominance. In the summer of 2021, with the emergence of the first significant variants, we began a Beta containing bivalent vaccine arm. In February and March of 2022, we enrolled the group to evaluate the BA.1 containing bivalent vaccine. And in August of 2022, we enrolled the group to evaluate the BA.4/5 containing bivalent vaccine. Both Omicron containing vaccines were administered as a fourth dose and compared to the fourth dose of the original vaccine, a cohort enrolled in February of 2022. As the study was open label, hypothesis testing was conducted using a non-contemporaneous control. The pre-specified immunogenicity endpoints of the study were aligned with FDA guidance. We reviewed the BA.1 bivalent vaccine data at the June 2022 VRBPAC, and now I will present the BA.4/5 data.

The BA.4/5 bivalent vaccine cohort in this study included 511 participants. At the time of the interim analysis, follow up was for 37 days post booster. Here are the demographics of the BA.4/5 bivalent and the non-con contemporaneous original vaccine control group. There was significant representation of those over 65 in both groups, and as the pandemic involved, more participants had evidence of prior SARS-CoV-2 infection in the BA.4/5 bivalent group, enrolled in August, compared to the original vaccine group, enrolled in February. Hypothesis testing was done, therefore, in the subgroup with no SARS-CoV-2 infection, as pre-specified in the protocol.

Here are the neutralizing antibody results with the validated BA.4/5 assay. The BA.4/5 containing bivalent is in the dark blue. The original vaccine is in the mediblue. The left panel is for those with no prior SARS-CoV-2 infection, the primary analysis, and the right is for those with prior infection, and on the bottom are the geometric mean ratios. The BA.5 bivalent met the pre-specified superiority criteria compared to the original vaccine, with a geometric mean ratio of 6.3. And these results are consistent in those with evidence of prior SARS-CoV-2 infection.

Recognizing that adults 65 and older have the greatest risk of morbidity and mortality with COVID-19, we also analyze the data by age. As you can see, the 65 plus population had a robust response with the BA.4/5 containing bivalent vaccine that was similar to the 18- to 64-year-old group.

Next, we look at cross neutralization data for the Omicron subvariants, which have continued to emerge and are now dominant in the US. It is important to note that these variants retain the mutations of prior variants, and therefore were closer to Omicron BA.4/5 than the original Wuhan strain.

Here are the cross-neutralization data run in a qualified assay using the same methodology as our pseudo virus neutralization assays. BQ1.1 is on the left, XBB.1 is in the middle, and XBB.1.5 is on the far right. For all the variants, significant cross neutralization titers were detected in both participants without and with prior infection. As expected, those with prior evidence of infection had heightened titers.

Now, we also initiated a large, randomized, double-blind active controlled trial in early 2022 to examine the BA.1 monovalent and bivalent booster vaccines compared to the original vaccine. This study was conducted in the United Kingdom. Part one of the study was smaller and evaluated the BA.1 monovalent vaccine, and part two was larger and evaluated the BA.1 bivalent vaccine. The results for both parts of the study were made public yesterday in a preprint article. In the interest of time, I'm focusing my presentation on part two, evaluating the BA.1 bivalent vaccine, because of the larger sample size, and because this vaccine was the one authorized in the UK.

In this graphic, we show the enrollment of part two of the trial superimposed on the variant waves in the UK. Enrollment was from March through June of 2022. More than 2,800 participants were enrolled in the part two of the study. The primary objective of the study was to evaluate the safety and also the immunogenicity of the variant vaccines compared to the original vaccine. A secondary objective of part two was to compare the incidence rate of COVID-19 in the bivalent versus the original vaccine groups. The study was powered, though, on the immunogenicity objectives, and not to detect a difference in the incidence rates.

The mean age in both groups was 57 years, and about a third of the population was 65 and older. 25% of participants had evidence of prior SARS-CoV-2 infection. The median interval between third and fourth dose was about five months, and most participants had received an adenovector primary series followed by another mRNA vaccine as a first booster.

The booster dose of the Omicron BA.1 bivalent vaccine met all pre-specified endpoints, including superior neutralizing antibody response against Omicron BA.1, with the geometric mean ratio of 1.5. The GMR was very consistent with what we observed in our open-label study, study 205, with the same BA.1-containing bivalent vaccine presented at the last VRBPAC.

Although the study was not sufficiently powered to detect differences in incidence rates numerically lower COVID-19 incidence rates were seen in the bivalent group, in green, versus the original vaccine group, in blue. The incidence rates diverge at about day 40 post-vaccination, during the BA.2 wave in the UK, and the difference is maintained through 120 days of follow-up.

Since we continuously sequence SARS-CoV-2 infections in our clinical trials, we were able to analyze COVID-19 incidence rates by the Omicron sublineage. An exploratory analysis

of BA.2, BA.4, and BA.5 subline lineages showed a lower incidence rate in the BA.1 bivalent arm compared to the original vaccine for the BA.2 and BA.4 sub lineages on top. This trend was not seen for the BA.5 sublineage group, which further antigenically diverged from BA.1 and demonstrated increased infectiousness versus BA.4. The relative efficacy favors the BA.1 bivalent vaccine for the non-BA.5 five strains, but is similar to the original vaccine for the BA.5 strains.

Next, we have the evaluation of the bivalent vaccine as a primary series. This occurred in study 306, which was set up in June of 2022, due to ongoing discussions on bivalent vaccines. At this time, the BA.1 vaccine was available for clinical trials. We chose to evaluate the bivalent primary series in this youngest age group of six months to five years because this is the population in which data are most needed from a for a primary series going forward. It is expected that the findings here can be extrapolated to other age groups.

The study 306 evaluation of the primary series builds on the historical control from our previous study in this age group, study 204. Study 204 enrolled more than 4,700 children and was the basis of primary series authorization in this age group. In study 306, we plan to enroll around 480 children. An interim analysis of the study was performed with 179 children to facilitate the primary series discussion today. The immunogenicity was pre-specified to be compared to the historical control from study 204, and the safety art data are presented side by side with both post-dose one and post-dose two data with the original vaccine primary series.

The children enrolled in the bivalent vaccine primary series had a mean age of three, and 60% of these children had evidence of prior SARS-CoV-2 infection reflecting the rising seropositivity in unvaccinated groups.

These are the reported local solicited adverse reactions. The bivalent vaccine primary series is in green, compared to the original vaccine, in blue. There were no major differences from the original vaccine primary series, and there were no grade four events. Here's the systemic reactogenic now, reported after a primary series in children 37 months to five years. Fever is similar at 13% post-dose two in the bivalent group, and 16% post-dose two in the original vaccine group. No grade four events were noted in the bivalent group. And here is the systemic reactogenicity events reported after a primary series in the youngest children, 6 to 36 months. Again, fever post dose two is similar at 14%, and no grade four events were noted.

Now, here is the immunogenicity comparison. For this study, due to the predominance of prior SARS-CoV-2 infection, the immunogenicity hypothesis testing included all participants regardless of baseline SARS-CoV-2 status. On the left, the BA.1 immunogenicity is significantly higher for the bivalent vaccine compared to the original vaccine with the geometric mean ratio of 25. And on the right, the responses against the original strain were similar between the bivalent and the original vaccine, with the geometric mean ratio of 0.8. Both the co-primary endpoints for superiority against BA.1 and non-inferiority against the original strain were met.

We have previously compared baseline sernegative populations and other studies. A pre-planned analysis of the sernegative group in this study showed consistent results for the BA.1 responses. A reduced response to the original strain was seen for the bivalent group. Recall that the original vaccine was about 30 to 50% efficacious in this age group, with efficacy assessed during the Omicron wave. We expect that a bivalent primary series would provide better protection against the currently circulating Omicron variants.

Real-World Effectiveness Data

Dr. Das: Now, results from a number of real-world effectiveness studies have been presented earlier today. Here, I will discuss results from our ongoing study of the Moderna BA.4/5 bivalent vaccine at Kaiser Permanente. This matched cohort study included 157,000 individuals boosted with the Moderna BA.4 bivalent vaccine, who previously received at least two doses of an original mRNA vaccine. A relative vaccine effectiveness, comparing the BA.4/5 bivalent vaccine with individuals who had two or more original vaccine doses, was 73% for chart confirmed hospitalizations for COVID-19 and 56% against ED and urgent care visits.

Vaccine effectiveness of the bivalent booster also was demonstrated when compared to individuals not vaccinated with any COVID-19 vaccine. These data support that Moderna's bivalent BA.4/5 Booster provides additional protection compared to those who did not receive the bivalent booster.

We recognize that FDA has identified a number of critical evidence gaps. Our clinical development program includes trials designed to address some of these gaps, including long-term safety and immunogenicity data after primary series and boosting with bivalent vaccines, bivalent boosters administered annually, primary series in younger infants, younger than six months of age, and a single dose primary series. I will now turn to Dr. Edwards to discuss our preclinical data from variant-containing vaccines.

Preclinical Results from Authorized and Investigational Multivalent Vaccines

Dr. Edwards: Thank you, Dr. Das. Good morning. My name is Darin Edwards, and I am Senior Director of Translational Immunology and non-clinical research leader of COVID-19 vaccines at Moderna. Moderna continuously monitors for emerging variants and classifies variants based on the incorporation of innovating mutations and on the measured growth dynamics of these emerging variants. For those that meet our pre-specified criteria, preclinical mRNA materials are prepared, and key manufacturing steps are initiated as soon as possible to prepare for the possibility of vaccine update requests from health agencies. An example of this process is our preparation for three currently circulating variants, which we began in early fall of 2022. These efforts are performed to allow for expedited delivery of new vaccines should they be requested. An example of the benefit of this ongoing effort was seen in Moderna's rapid development of the BA.4/5 booster vaccine.

The BA.4/5 Boost bivalent vaccine preparation had begun in spring 2022 based on our epidemiological monitoring and variant risk assessment efforts. Subsequent to the FDA's request for a BA.4/5 bivalent vaccine in June of 2022, preclinical evaluations were completed, and large-scale manufacturing batches were prepared. This rapid development and evaluation enabled authorization in late August, and initial vaccine supply was subsequently released. This also highlights Moderna's preparation for an annual vaccine selection process in our ability to respond quickly for an off-cycle update, should an immune-evading variant merge.

Moderna's ongoing monitoring and variant response effort has enabled the development and evaluation of more than 19 monovalent and bivalent vaccine compositions. In addition, through our real-time monitoring efforts, we have started our development and evaluation process for three recently emerged variants, XBB.1, BQ.1.1, and BN.1. In our preclinical evaluation of these new variant vaccines, we're not only assessing monovalent and bivalent

vaccines, but also novel bivalent combinations, those that include the original strain and also those that do not. These novel bivalent compositions are listed.

Moderna's authorized original strain and bivalent BA.4/5 vaccines were evaluated in a primary series mouse immunogenicity study to evaluate the breadth of neutralization across variants that each vaccine provided. The original vaccine provided significant neutralization against the matched ancestral strain, but significantly less breadth of neutralization against Omicron lineage variants that have more recently emerged. By contrast, immunity generated from the vaccination with BA.4/5 bivalent vaccine provided robust breadth of neutralization against multiple variants, as well as the original strain. Now I will turn the presentation back over to Dr. Das.

Summary and Conclusions

Dr. Das: Thank you, Dr. Edwards. In summary, our BA.4/5 bivalent vaccine booster met all pre-specified immunogenicity endpoints, and the results were consistent for the 18 to 64 and the greater than 65 years groups.

The randomized, active controlled study in the UK with the BA.1 bivalent vaccine compared to the original vaccine confirmed the immunogenicity and safety conclusions with the same vaccine in the US Open-Label study. Although the study was not sufficiently powered to detect differences in Covid incidence rates numerically lower Covid incidence rates were seen in the bivalent group versus the original vaccine group. An exploratory analysis of the relative efficacy favors the BA.1 bivalent vaccine for the non-BA.5 strains but is similar to the original vaccine for the BA.5 strains. Cross neutralization also has been observed for emerging Omicron

subvariants. Primary series with BA.1 B valent vaccine met immunogenicity endpoints and was well tolerated in children. And real-world effectiveness data from the Kaiser Permanente study confirm additional protection from hospitalizations and ED urgent care visits with the BA.4/5 bivalent booster.

As SARS-CoV-2 continues to evolve boosters with bivalent vaccines can protect against infections when the variants are more closely related but continue to protect against severe disease even as the variants diverge. We will continue epidemiologic monitoring and risk assessment of emerging variants and subvariants and will evaluate candidate vaccines as needed. We remain committed to providing data and manufacturing readiness to support timing and composition decisions for harmonized updates to boosters and primary series.

I'd like to thank our study collaborators, investigators, and most importantly, all of the participants in these trials. And again, I'd like to thank the committee for the privilege of presenting to you today. We would be happy to address your questions.

Q & A

Dr. Perlman: Thank you very much for a clear presentation. So we have time for a couple of questions. I just want to ask one quick one first. So you have differences between BA.4 and BA.5 in terms of clinical efficacy, but they have identical S proteins. So how do you explain that?

Dr. Das: Yes, I will start, and I can then turn it to Dr. Edwards. We do believe that the BA.5 has — As BA.5 has dominated worldwide, we know that the BA.5 has a fitness and an

infectiousness advantage over the BA.1, over BA.4, which is evidenced by the kind of the size of the different waves that were — the size of the respective waves that the world saw. Also, you know, the BA.5 wave did come later during this study. Dr. Edwards, is there something else you would like to add to that? No. Okay.

Dr. Edwards: Okay. Thank you, Dr. Levy.

Dr. Levy: Hi. Hello. Can you hear me?

Dr. Das: Yes.

Dr. Levy: Yes, my question is for Dr. Das. Thanks for a very clear presentation. I had one question on safety and one on immunogenicity. The safety data you presented for the BA.1 bivalent, by eye, it seemed that there was reduced reactogenicity in many of the RA reactogenicity endpoints. Do you have any insight? Does Moderna have any insight as to why the reactor would be lower and what lessons can be learned from that moving forward?

And then the question around immunogenicity relates to our discussion with Dr. Beigel about correlates of protection. Will Moderna be conducting nested T-cell immunogenicity studies and present those at future FDA meetings? Thank you.

Dr. Das: Yes, thank you for the question. So for the safety question first, we have seen across our bivalent vaccine programs the decreased, a little bit decreased reactogenicity. It's, you know, it's nothing that's significant, but the trends do fall that way. We have the, I believe the randomized trial, so these are non-con contemporaneous, but the randomized trial of the 305 booster kind of showed the same thing. We're not quite sure why this the reason for this, but, but I think it's, it is a finding that we have seen consistently.

In terms of the correlates of protection analysis, you know, we are very, we supported the correlates of protection analysis with the COVES study that that Dr. Beigel described. And we are continuing to work with our colleagues to look at variant-specific correlates of protection. So we'll be starting next with an Omicron BA.1 correlates of protection study. We are, though, limited in these studies by what samples were taken so far. And so in the majority of the COVES study it was sersamples. And so neutralizing antibodies are the largest, make up the largest portion of our correlates of protection work. We are, we have studied T-cell responses and we will continue to include these in studies as feasible, but I think our current work will have to be on the serologic correlates, which although they may not be a mechanistic correlative protection, they are correlated with protection, which we have seen in the original strain and has been suggested for the variants as well.

Dr. Perlman: Okay. Thank you. Dr. Offit.

Dr. Offit: Yes. Thank you. This question is for Dr. Das. First of all, I want to commend you for doing that study in the UK where you could actually control for the length of time between booster doses with the monovalent and the bivalent vaccine, which then eliminated a lot of the confounding variables that were seen in the study is done in this country trying to compare bivalent with monovalent. But I noticed it in that study that you referred to, the UK study, there were three arms, which was not just the ancestral strain alone in the monovalent or the bivalent with ancestral plus BA.1. There was also a BA.1 only arm with, with 50 micrograms of mRNA. I just wonder if you could comment on that. Because it really gets at the question that hopefully we'll address at some point, which is, do we need to continue to have the ancestral strain mRNA in these vaccines? Thank you.

Dr. Das: Yes. And I can, we can bring up the slide for the immunogenicity of the monovalent BA.1 vaccine arm as well as the bivalent arm. And this is all in the preprint that was posted yesterday. But you see the, so on the on the left part of the slide is the monovalent, the purple is the BA.1 only, and on the right side of the slide is the BA.1 bivalent.

And you see those geometric mean tighter ratios on the bottom. And so they, they each have an individual, they're each randomized to their respective original vaccine. And so you see the geometric mean titer ratios on the bottom are very similar. 1.7 and 1.5. But if you look at the if you look at the, well, yes, here we go. But if you look at the original strain data here, the responses to the ancestral strain, you do see that there seems to be some benefit for the bivalent vaccine there. The geometric mean ratio is 0.8 versus 1.0. You know, whether this — in our, in our other studies, we have shown that using a bivalent, you can perhaps diversify the immune response that you get in order to kind of try to prepare or be closer to the ongoing evolution. And perhaps this gets at that benefit for the bivalent.

Dr. Offit: Thank you.

Pfizer Presentation

Dr. Perlman: Thank you. I think we need to uphold the rest of the questions until the later period when the sponsors will be back because of our tight schedule. So I think we need to move on to the next presentation by Pfizer. So this is going to be presented by Dr. Swanson.

Pfizer/BioNTech COVID-19 Variant Vaccines

Dr. Swanson: Hello, good afternoon. My name is Kena Swanson, and I'm head of Viral Vaccines R&D at Pfizer. On behalf of Pfizer and BioNTech, it is my pleasure to share our perspective on the future vaccination regimens for COVID-19. Through our extensive evaluation of monovalent and bivalent variant modified vaccines, the safety profile has remained similar to the original vaccine, as you heard earlier today, and the vaccines performed in humans as the preclinical data predicted. For the purpose of today's presentation, I will focus on recent data for our bivalent Omicron BA.4/5 modified vaccine, the first update to the original vaccine in response to the substantial antigenic shift of SARS-CoV-2 that occurred with the emergence of the Omicron variant. I will end with a view of how we are poised to respond to emergent strain changes when needed, and together with shifting to a more regulated annual strain change process for future COVID-19 vaccine updates.

Vaccines that are better matched to circulating strains have a critical role to play in the ongoing public health response to COVID-19. In the United States, there has been an increase in Covid-associated hospitalizations corresponding to the winter respiratory season months of November through March. As shown in the figure on the right, cases surged in January 2021 due to the Alpha variant, and again in January 2022 following the emergence of Omicron. Vaccines continue to be the most effective approach for prevention of COVID-19. Variant vaccine compositions more closely matched to circulating strains can restore waning immunity against hospitalization. And this was first observed with the bivalent Omicron BA.4/5 vaccine update in fall 2022, which was triggered based on immunity waning around three to six months after

vaccination with original vaccines. Compared to less well-matched vaccines, they offer increased protection against currently circulating strains for both neutralizing activity and real world clinical outcomes. As presented by the CDC earlier today, the bivalent BA.4/5 mRNA vaccine has improved protection by roughly 40 to 80% relative to the last dose of original vaccine during periods predominated by BA.5 and BQ.1.1 sublineages, with higher effectiveness seen against more severe outcomes like hospitalization. The most recent data from CDC also show that effectiveness of the bivalent vaccine is maintained against symptomatic disease caused by XBB sublineages.

Now taking a closer look at our variant vaccine experience. This is included evaluation as both a primary series and booster. Shown on this slide with the original B&T162V2 vaccine, in blue, and variant vaccines shown in purple, and starting at the top with the monovalent Beta variant vaccine. Across the data generated to date, including evaluation of bivalent Omicron BA.4/5, preclinical data have reliably predicted the responses in humans, and as we presented in June and will share further evidence today, variant vaccines show improved responses compared to the original vaccine as a booster dose. For a primary series, the monovalent Omicron BA.1 vaccine has shown an Omicron-specific response in humans. However, pre-clinical studies suggest bivalent vaccines may confer a broader neutralizing response across variants of concern compared to monovalent formulations. The bivalent Omicron BA.4/5 vaccine, which contains mRNAs encoding the original and Omicron BA.4/5 spike, was authorized in August 2022 based on clinical safety and effectiveness for the original vaccine and clinical safety and immunogenicity for the Omicron BA.1 modified vaccine, together with preclinical data for the bivalent BA.4/5 vaccine. As part of a post-authorization commitment, we are conducting clinical studies to generate safety and immunogenicity data across multiple age groups.

First, I will describe the study in participants 12 years and older. Shown here as a clinical study evaluating the bivalent vaccine at a 30-microgram dose level as a fourth dose booster in vaccine-experienced individuals that received three prior doses of the original B&T162V2 vaccine. Indicated in purple below, we assessed immune responses following a bivalent booster dose in adolescents 12 to 17 years of age and adults 18 to 55 and greater than 55 years of age. Immune responses were compared following a booster with either the bivalent vaccine or the original vaccine among participants greater than 55 years of age. The original vaccine comparator group, shown in blue on the bottom right, was part of a previous vaccine study. COVID-19 disease surveillance was also part of the study, but as the original vaccine group is a historical comparator, no contemporaneous control was available to assess potential efficacy.

Presented here are the demographics for the three bivalent vaccine groups and the original vaccine comparator group. Age distribution was as expected based on the enrollment criteria, and the ratio of males to females was consistent across the groups. Focusing below, note that prior SARS-CoV-2 infection among participants was confirmed by either medical history, serology, or RTPCR just prior to administration of the fourth dose booster to discern immune responses in those positive or negative at baseline. Bivalent vaccine groups received the booster dose in fall of 2022 and had a similar proportion of those with prior infection. The B&T162V2 group, to the right, was boosted in spring 2022 and thus had a lower proportion of individuals positive at baseline. The bivalent booster was administered a median of approximately 8 to 11 months following dose three, and the original vaccine booster was administered a median of approximately 6 months following dose three. Despite differing time intervals, the baseline neutralizing titers prior to the fourth dose booster in adults were generally similar when matched by infection status.

To meet the primary endpoint of the geometric mean ratio, or GMR, for the BA.4/5 response of bivalent and original booster doses in participants greater than 55 years of age, superiority for the Omicron BA.4/5 response was to be established between the bivalent and original vaccine groups based on the GMRs. And for the secondary endpoint of GMR for the reference strain response, non-inferiority was also to be established. Given the potential variability in SARS-CoV-2 infection experience, all comparisons between vaccine groups were based on a linear regression model that controlled for baseline neutralizing titers. Data from a validated SARS-CoV-2 live virus neutralization assay demonstrate that the GMR success criteria were met for the bivalent vaccine. Shown on the right, with a GMR of 2.91 and lower bound of 2.45, superiority was met for Omicron BA.4/5. And for the reference strain, below, a GMR of 1.38 and lower bound of 1.22, showing non-inferiority was met. Finally, summarized in brief at the bottom of the slide, non-inferiority of the sera response was also met, with sera response defined as achieving a greater than or equal to fourfold rise from baseline, and requiring the lower bound of the 95% confidence interval for the percentage difference in sera response between the bivalent vaccine and original vaccine group being greater than -5.

Next, we evaluated whether responses to the bivalent booster were similar between the two adult age groups. Assessing responses in those with or without evidence of prior infection, BA.4/5 neutralizing responses were similar between younger and older adults, shown on the right with a GMR of 0.98, meeting the non-inferiority criterion. And shown below, in blue, non-inferiority of the sera response was again also met. In this comparison, we're requiring a lower bound greater than -10 for the percentage difference in sera response between the younger age group and those greater than 55 years of age.

In addition to the formal analysis of the Omicron BA.4/5 neutralizing response shown here are the geometric mean titers, or GMTs, indicated above each bar, and in the box above the geometric mean fold rise, or GMFR, from one month after the fourth dose compared to pre-dose four. Bivalent groups are in purple and the original vaccine group in blue, and the data are presented according to SARS-CoV-2 infection status at baseline. Three important trends are shown. Responses with the bivalent vaccine were substantially higher than the original vaccine. Those with prior infection had overall higher titers, and the immunological benefit of the bivalent vaccine was conferred regardless of baseline infection status. And this was consistently observed across the three age groups and supports that, even if you have been previously infected, there remains a clear benefit to receiving the bivalent booster. We also continue to monitor the variant landscape to understand neutralization activity against new strains as they emerge.

Here we show data comparing the bivalent and original monovalent vaccine neutralizing activity against more recent Omicron sublineages. These data are now published in the New England Journal of Medicine. A descriptive analysis of Omicron BA.4/5, BQ.1.1, and XBB.1 from a subset of participants greater than 55 years of age is shown using a SARS-CoV-2 fluorescent focus reduction neutralization assay. Data for participants without prior infection are shown on the left and in participants in those with prior infection are shown to the right and represent approximately 20 individuals in each group. Improved responses regardless of the prior infection status were observed against all the Omicron sublineages tested. For example, for BQ.1.1 on the left, a GMFR of 12.6 for the bivalent vaccine versus 1.5 for the original vaccine. Neutralizing activity against BQ.1.1 is modestly reduced compared to BA.4/5 and more substantially reduced against XBB.1. Initial reports and our own recent data show that

neutralizing activity against the newly predominant XBB.1.5 is similar to XBB.1. And data presented earlier suggests effectiveness is maintained against both BQ.1.1 and XBB sublineages.

Additional clinical studies in children younger than 12 years of age are also ongoing to evaluate the bivalent vaccine, not only as a booster, but, importantly, as a primary series. The evaluation of the primary series is ongoing. Today I am pleased to share initial data in children younger than five years of age for the booster dose.

Shown here is the design for the booster study that includes B&T162V2 experienced children six months to less than five years of age, who received the three dose primary series of the original vaccine at the three microgram dose level. Safety and immunogenicity has been assessed in a subset of 60 participants, where the bivalent booster was administered a median of approximately six and a half months following dose three of B&T162V2. The booster dose was administered in fall of 2022. A descriptive analysis was performed assessing responses following the bivalent fourth dose booster compared to a control group that received three doses of the original vaccine.

Here, the bivalent vaccine group is shown on the left, in purple, and the original vaccine on the right, in blue. Vaccine groups were matched by age, baseline infection status, and interval from prior vaccine dose. In participants six months to less than five years of age, the Omicron BA.4/5 responses were substantially higher in the bivalent vaccine group after the fourth dose compared to the control original vaccine group After the third dose, with a GMT of 1700 versus 600. Now shown for the whole group and divided by age subgroups, responses were similar for children six months to under two years, and children two to less than five years of age. These data provide further support and assurance of the improved immune responses with the bivalent vaccine for all ages. Evaluation of the bivalent BA.4/5 vaccine as a primary series is ongoing

within this pediatric study in children six months to five years of age, and results are anticipated in the coming months.

As we have observed in prior clinical studies, the reactogenicity profile of variant vaccines continues to be consistent with the original B&T162V2 vaccine. This is supported by the large volume of post-authorization global safety data, and we continue to perform surveillance on safety data from all sources, working closely with regulatory and public health authorities around the world, including the CDC. The overall benefit risk profile for the original and the bivalent vaccine in authorized populations continues to be favorable.

To summarize the effectiveness data presented today, the bivalent vaccine met superiority and non-inferiority criteria in the post-authorization clinical study, and has demonstrated improved effectiveness against circulating Omicron sublineages, including BQ.1.1 and XBB. The immune response data are consistent with real world benefits observed in the general population.

So where do we go from here? We want to mitigate against potential for waning immunity and maximize protection against future variants. There are a number of factors to consider in preparation for and deployment of COVID-19 vaccine updates. Real-world effectiveness data and potential changes in disease severity continue to be monitored but are information that may arrive too late for a vaccine update to have maximal impact at improved protection. Ongoing evidence collection will be key to inform early reads on the need for a vaccine update. These include assessing antigenic distance of circulating strains relative to the current vaccine, the degree of immune escape, and potential approaches that may better overcome immune imprinting. Broad versus more localized distribution of new variants and the degree of transmissibility are also hallmarks for the potential need to respond. A library of

candidate vaccine constructs prioritized by these data and prepared at risk could be available for a vaccine update based on early evidence. The vaccine composition could include monovalent or higher valency vaccines dependent upon the factors described.

Now, moving forward, COVID-19 may ultimately transition to a seasonal, endemic disease, peaking in winter like influenza and RSV, but we will also need to be prepared for potential off-season disease caused by new or rapidly changing variants. This means that a model for COVID-19 vaccine updates requires adaptability and an established pathway to licensure. Pfizer and BioNTech support FDA's proposal that the current pathway established for annual influenza vaccine updates could be adapted to enable annual COVID-19 vaccine updates. The current influenza model is shown for reference in gray. Restrained selection occurs in February for the US and other northern hemisphere regions several months prior to vaccine distribution in fall. Licensure of seasonal influenza vaccines occurs in July and is based on nonclinical and manufacturing data only. No clinical studies are required to support licensure.

Shown below in blue is one example for a COVID-19 update model, positioning strain selection closer to the season, which would allow manufacturers to more closely match the COVID-19 vaccine to strains in circulation. Again, an off-cycle update could also be supported if needed and based on the dynamics of variant epidemiology. Licensure would be supported based on our extensive clinical experience across four variant vaccine formulations to date, translatability of preclinical data to humans, and a pre-specified data package to support a vaccine update. Using the proposed pathway, the timeline from strain selection to vaccine availability could be approximately 100 days, as we recently demonstrated in the first vaccine update. The time is now to define the strain selection process, the regulatory requirements, and pathway for licensure of future variant vaccine updates for booster and primary series

vaccination. And this will help maintain optimal protection against COVID-19 and enable a rapid and coordinated public health response to emerging variants.

To conclude, variant-modified vaccines continue to show a favorable safety profile with improved effectiveness for the bivalent vaccine against COVID-19 through periods of Omicron BQ.1.1 and XBB predominance. As seen with influenza and now with COVID-19, vaccines more closely matched to circulating strains offer improved protection. Recent reports showing improved effectiveness for the bivalent Omicron BA.4/5 vaccine compared to the bivalent Omicron BA.1 vaccine support this. An established model for future variant vaccine updates will be an important first step to better address COVID-19. But we know our work is not done. Next generation vaccine candidates aim to enhance both the breadth and duration of protection that could potentially yield a variant proof vaccine, and importantly, minimize the frequency of boosters. We look forward to today's discussion on these topics.

Pfizer and BioNTech wish to thank the clinical trial participants and their families, the site's investigators and CRO, our partners and their staff, and the FDA, as well as the VRBPAC Committee. Thank you for your attention. My colleagues and I will now be happy to take questions.

Q & A

Dr. Perlman: Thank you, Dr. Swanson. So we have about eight minutes for questions. Dr. Sawyer?

Dr. Sawyer: Thank you for updating us on your progress. One of the challenges we face today is deciding if we have enough information on using the bivalent vaccine as a primary series. That is particularly true for the youngest children under two years of age, whose immune response may not be the same as older children or adults. I noticed in your bivalent booster study you only had 20 children, if I read the slide correctly, in that youngest age group. Can you tell us, in your ongoing primary series study, how many children under two are you going to have data on, in time for this 100-day window by which we can make a choice of which vaccine to give?

Dr. Swanson: Thank you for the question. And we are very keen to understand the performance of the bivalent vaccine in the pediatric population. I'll ask actually, Dr. Charu Sabharwal to come up and elaborate in more detail. The data we included in today's presentation is what is currently available on a subset of children from the ongoing pediatric study. So 60 children overall, and approximately equal numbers between the two age groups, the younger children and the older children. But Dr. Sabharwal?

Dr. Sabharwal: Thank you, Dr. Swanson. It's Charu Sabharwal from Pfizer Vaccines. For our primary series phase one study, we will have 90 participants in the six months to less than two-year-old age group, and an equal amount will also be in the two to less than five-year-olds. And to circle back to the booster, just to share that we will ultimately enroll 300 participants in that age group. Thank you.

Dr. Sawyer: Thanks.

Dr. Perlman: Okay. Thank you. Dr. Gans?

Dr. Gans: Thank you for this presentation. I had a question, sort of a comment on your comment that we have to quote think about imprinting. And I don't actually see evidence in any

of the booster data for this notion. There were some, there are a couple of papers — this is controversial, I understand, but at least from your standpoint, I would love to understand where that comment is coming from. That's my first comment. My second one is, when we're considering new vaccines and new whatever, if it's going to be bivalent, monovalent, are dosing consideration going to be undertaken again? As we know that two three doses — in the children is what I'm particularly interested in, since three doses is part of the primary series, and that might have to do with the dosing that was considered for those original studies. Thank you.

Dr. Swanson: I'll start with the first question about imprinting and where I would start is to say that we do know from the totality of the data that, when you have an Omicron component within the vaccine, you do confer improved responses against Omicron and its sublineages. So there is a benefit, but we also know the history. And here I'll reference probably influenza, where there's a much more extensive year to year data of where there may be some potential immune imprinting and how can you best overcome that. So I think, you know, we're looking at all of the data and going forward we'll continue to generate more to better understand how much of a hurdle that may or may not be for SARS-CoV-2.

For the second question on two versus three doses. So the ongoing pediatric study evaluating the primary series is evaluating — well, we will have data generated after the second dose as well as three doses of the bivalent vaccine. And knowing that as the variants change, it's a moving target. And the current dose level for the original vaccine in the pediatric population is three microgram. But we also want to understand, as you're changing these vaccines, do they perform the same way? So there is also a dose ranging component within that primary series portion of the pediatric study.

Dr. Gans: And it includes higher doses?

Dr. Swanson: Yes.

Dr. Perlman: Okay. Thank you. Dr. Gellin?

Dr. Gellin: Thanks all. Thanks for all these, I'm glad they're being recorded. I'm not sure who's going to watch them again, but they're good to have, so thanks for thanks for that. Questions about production for both manufacturers. Pfizer's gave us a hundred-day marker. We didn't hear a similar number from Moderna. I'll assume it's the same, but what if the — if we're going to think about the flu model, what if we talked about 2, 3, 4 valents? In June, we said we need that. We need those flavors. What's feasible in that situation? And then, I'm not clear what your production facilities are, but since this is a, even though the briefing document talked about coordination with WHO, if we order, the United States orders, these valent vaccines in June, does that mean that's what the rest of the world's going to get without having had a chance to order something different?

Dr. Swanson: I think on the last point, I'll, I'll maybe wait for this afternoon's discussion between FDA, CDC, and the committee on how the global coordination may look like going forward. But I will ask my colleague here, Bill Falstich, here in a second to elaborate on the supply question. But I will, just to start, remind, last year we were in the face of deciding Omicron BA.1 versus Omicron BA.4/5 vaccines. And so Pfizer and BioNTech were supplying both of those vaccine formulations based on the different areas and countries that were requesting them.

Dr. Perlman: Okay. Thank you, Dr. McGinnis.

Dr. Falstich: Hi, good afternoon. Bill Falstich. I'm the Vice President of Global Supply Chain here at Pfizer. On the first question, could the hundred-day timeline be similar if we had, let's say

more than two components to the vaccine? Yes, it, it could be, we have the production capability to enable that in a similar, roughly 100-day timeline. And then as to the second portion of the question, if the US makes a decision in June would that bind the world to a similar decision cycle. The answer's not, not necessarily. So as Dr. Swans mentioned, this past year, we delivered BA.4/5 hello bivalent to US. We delivered a BA.1 bivalent elsewhere in the world. It was on separate decision cycles, and we were able to manage that with no concerns and fulfill all the global demand. So we could be flexible like that again if we needed to.

Dr. Perlman: Okay. Thank you. Dr. McInnes.

Dr. McInnes: I'm sorry. I thought I was called upon and then somebody else interrupted me.

Dr. Perlman: No, it was my fault, because I called on you before the Pfizer had finished answering the question.

Dr. McInnes: Hmm, interesting. Well thank you. So I have a couple of comments. Can you hear me right now?

Dr. Perlman: Yes.

Dr. McInnes: Okay. I'm going to put my video on so you can see that I'm authentic. Yeah. Hello. So I have some basic questions for Pfizer about what data they have that they could lay out between the bivalent and the monovalent in terms of protection from infection or disease. I haven't actually seen those data. And then I have a question about this whole meeting focused on mRNA vaccines. So I think mRNA vaccines have been phenomenal in dealing with the initial problem, but we seem to be tracking along the same path. And so I want to know about any kind of approach. And so, you know, for bivalent and monovalent, we haven't seen randomized

comparison trials to demonstrate superiority. And then I don't want this meeting to be hijacked by mRNA vaccines. So I guess that's my comment. Thank you.

Dr. Perlman: Yeah. So just to answer the second part, our next talk is by Novavax, which will have a different formulation. And maybe, Dr. Swanson, if you can answer the first part quickly, because we're running out of time.

Dr. Swanson: Yeah, I will keep it brief. I'm not aware of any head-to-head efficacy or effectiveness data between monovalent and bivalent formulations. What I can say is we do have clinical data from the randomized controlled trial that compared monovalent Omicron BA.1 vaccine versus bivalent Omicron BA.1 vaccine, and both formulations induced superior neutralizing responses compared to the original vaccine as a fourth dose booster. There was a trend for higher responses with the monovalent vaccine. We don't know whether that is clinically meaningful or not. You know, in the presence of you know, the discussion that was had earlier this morning around correlates of protection, I think that's still a moving target. It's not clearly established. But those are the data that we have.

Novavax Presentation

Dr. Perlman: Good, thank you. So I thank you, the Pfizer team, again for their answers. And I think we need to move on to the third presentation by Novavax. And this is going to be given by Dr. Dubovsky, the Executive Vice President.

Novavax Vaccine Regimens Addressing COVID-19

Dr. Dubovsky: Good afternoon. My name is Philip Dubovsky, and I'm the Chief Medical Officer at Novavax. Today I'll present data on how our vaccine performs against variants and the implications for future strain selection. In this presentation, I'll describe our vaccine technology and features we think are responsible for the production of broad and long-lived immune responses. I'll show you data that our monotype strain vaccine induces broad responses when uses a homologous or heterologous boost, including against drift variants such as BA.1 and BA.5. These responses hold steady whether our vaccine is a prototype strain vaccine, a monovalent variant vaccine, or a bivalent vaccine. They all seem to work equally well, once again against board drifted variants.

We believe the breadth of immune response is at least partially due to induction of functional immune responses to conserve sequences that are common between the variants. I'll show you structure function data that brings functional immune responses to the presence of these conserved epitopes. When it comes to BQ.1.1 and XBB, we do see alterations in these conserved sequences leading to diminished neutralizing antibody responses. These reduced neutralizing responses appear to be comparable to the reductions seen with other approved vaccines, signaling that now may be a time to change vaccine composition. We note from recent preliminary real-world effectiveness data that although the immune responses are reduced, the vaccines still perform well, especially against severe outcomes. And the updated vaccine strains will include the new repertoire of epitopes, and we believe our technology will continue to induce responses to future forward variants that arise from newly recommended strain.

As a brief reminder, the Novavax vaccine includes the full-length recombinant spike protein, shown here in red, presented in its native trimeric confirmation. We manufacture the antigen in insect cells, which have truncated glycans. And we hypothesize this facilitates epitope exposure to the immune system. And the antigen forms particles around a polysorbate core, shown here in blue, which improves antigen uptake and processing. Our antigen is co-formulated with our saccharin-based adjuvant, which is known to facilitate the induction of broad B-cell and T-cell responses. The combination of these factors leads to high levels of efficacy against a prototype strain as well as against variants as circulated during our initial phase three studies.

As I present some of our clinical data for the variants today, I'll reference correlates of protection for our vaccine. An independent analysis conducted by the US government COVID-19 response team and NIH scientists was performed to identify correlates of protection for our vaccine. Analysis was based on our US/Mexico phase three efficacy study, where the majority of Covid cases were caused by variants, mostly Alpha, with some Beta, Gamma, Epsilon, and Iota.

And overall the vaccine showed an efficacy of 90% including against these variants. Anti-spike IgG levels and pseudo neutralization titers were found to correlate with protection against PCR-confirmed symptomatic infections. Uniquely, our anti-spike IgG responses appear to correlate more strongly with protection compared to neutralizing responses. Although neutralization responses are important, we know from systems serology studies that the vaccine induces IgG antibodies capable of a range of immunologic mechanisms, such as FC-mediated phagocytosis. The causal protection thresholds for binding IgG and neutralization are displayed in the two tables at the bottom of the slide. The specific immunologic thresholds are associated with protection against PCR-confirmed mild, moderate, and severe disease, noted on the right-hand side of each table. And I will annotate some future slides with these thresholds.

Okay, let's look at some data from our clinical studies. First, I'll briefly review some homologous boosting data from our US/Mexico phase three study and describe the breadth of immune response, including against Omicron subvariants. Participants in the study received a two dose primary series of prototype strain vaccine and were boosted at age 11 months with one dose of prototype strain vaccine. On the left panel, you have displayed anti-spike IgG responses seen after two doses. This priming series induced antibodies that recognize the prototype spike with a lower level of antibodies against BA.1, BA.2, and BA.5. The right panel represents the antibody levels after a single boost, and high levels of antibodies are seen against all the variants. The differences between the BA.5 and prototype and the priming series, which is about twelvefold, decreased to only about fourfold after boosting. This horizontal line indicates the IgG levels seen in our phase three clinical trials that were associated with high degrees of efficacy. After boosting antibody levels to BA.1, BA.2, and BA.5 were all comparable to these protective levels.

Here we've displayed the immune response for participants who are infected with a prototype strain prior to receiving any vaccine. On the left-hand panel, we see that, prior to infection, there was an induction of low levels of antibody against prototype strain vaccine and an even lower level against Omicron subvariants. However, after receiving a two-dose series, these infection primed individuals increase their antibody levels 60- to 75-fold. Again, these levels, including for Omicron subvariants, approximate levels associated with protection in the phase three study. This analysis is important because the vast majority of the US population has been primed with infection and/or vaccination or both, and this represents a real-world situation.

Okay, moving on to our adolescent data. In this study, all participants received a two-dose primary series of prototype strain vaccine and were boosted with prototype strain vaccine

about 10 months later. On the left panel, we have displayed the neutralizing responses against prototype, Delta, BA.1, and BA.4/5 after two doses. After a single boost, shown here on the right, there was a significant increase in neutralizing responses against all the variants. Here I've overlaid the correlates of protection thresholds that I highlighted earlier. You can see that the neutralizing levels observed after boosting are predictive to be protected against BA.1 and BA.4/5.

Another way to look at these neutralizing immune responses to variants is through antigenic cartography, as was shown by Dr. Beigel. Antigenic cartography shows the relative magnitude of immune response against disparate variants induced by the prototype strain vaccine. Each of these large grid boxes represents a twofold difference in neutralizing responses. So one box is twofold different, two box is fourfold difference, and so on. On the left, we show neutralizing responses after the two dose priming series. And here we've annotated the distance between BA.4/5, in pink, and the prototype, in green. And this represents approximately a 28-fold difference. On the right, after boosting, the antigenic distance decreases 1.7-fold, which for all practical purposes represents a matched response. This indicates that when uses a booster, the immune responses are almost indistinguishable, regardless of strain, giving us confidence of maintained efficacy, again for the variants, including through BA.4/5.

Next, I'll discuss some heterologous boosting data from Study 311, a strain change study conducted in Australia using different Novavax formulations. All participants had previously received two or three doses of mRNA vaccine. After enrollment, they were randomized to be boosted with one of three vaccines: a prototype strain vaccine, an Omicron monovalent BA.1 vaccine, or a bivalent vaccine that contained the prototype strain plus BA.1. The study achieved its strain change endpoint. The data I'll present today is a descriptive analysis of the breadth of

immune response following this heterologous boosting and represents a convenient sample from the study. No statistical comparisons were pre-specified. The primary endpoint was measured in individuals who received three doses of mRNA vaccine, so that's the data that'll be presented. Demographics and baseline characteristics were well-balanced between the three arms. The racial profile is consistent with the general Australian population. In about half of each group, were shown to be infected by antigen serology or PCR. And as you can see, the was administered about 180 days after the final dose of mRNA vaccine.

So here I'll display the IgG responses in all participants measured against prototype strength in BA.1, which were included in the vaccine formulations, as well as BA.5, which represents a model forward drift variant. The key question I'll address on the next two slides is whether updating with Omicron, either as a monovalent or bivalent, adds to the breadth of immunity, especially forward drift immunity. In the first triplet, we see that the anti-prototype responses were comparable irrespective whether prototype strain vaccine, BA.1 vaccine, or bivalent vaccine were used as a booster. Numerically, the prototype strain induced a greater anti-prototype response.

The same is true for anti-BA.1 responses. In the middle triplet, you can see the magnitude of the anti-BA.1 responses were comparable, irrespective of which vaccine formulation was used as a booster. And finally, when we look at the forward drifted anti-BA.5 responses in the right hand side of the slide, we see that neither BA.1 nor the bivalent provided any additional benefit compared to boosting with the prototype strain vaccine. And here I've added the correlates of protection thresholds that were developed for recombinant protein homologous vaccination. When applied to these heterologous boosted cohorts, this suggested protective antibody levels were achieved for the prototype strain, BA.1, and BA.5.

The setup of this slide is similar to the previous slide, except this shows validated pseudo neutralization responses. Once again, their responses are comparable irrespective of which vaccine was used as a booster. For the BA.5 forward drift responses, shown on the right hand side of the panel, all formulations induced similar neutralizing responses with no additional benefit observed for either BA.1 or bivalent vaccine. And overlaid here again are the correlates of protection thresholds, which suggest that protective levels may have been achieved. From this data, we conclude that the prototype strain vaccine performs well when use as a heterologous booster, and our monovalent and bivalent vaccines induce similar immune responses against BA.1 and BA.5.

Okay, now let's look at some data from a different heterologous boosting study where we have information from the most recent variants. Study 307 was a lot-to-lot consistency study conducted in the us. In this study, we enrolled 911 adults who had no previous history of recent Covid infection and who had received a primary series or a primary series plus one booster to approved Covid vaccine. The last vaccine dose was at least six months prior to enrollment. After enrollment, all participants were randomized to be boosted with one of three different lots of Novavax prototype strain vaccine, and immune responses were measured at day 28. The study met its primary endpoint, with the three lots performing comparably, thereby demonstrating manufacturing consistency. The data I'll be presenting today is a descriptive analysis with the breadth of immune response following heterologous boosting with our prototype strain vaccine, and no statistical analyses were pre-specified. The majority of participants received either Pfizer over in a vaccine, but a small number were previously vaccinated with the Covid Novavax vaccine.

Because the study was not designed a priori to evaluate different boosting schedules and these samples were randomly selected from study population, some differences are noted in the baseline demographics. There are more females in the Pfizer group. There are more white and Hispanic participants in the mRNA groups, while there were more black or African Americans in the Novavax group. The median interval prior to boosting ranged from 33 to 61 weeks. However, the pre-boost titers were all clustered between 33 and 54,000.

Okay. First, let's look at the IgG responses to the prototype strain. We're displaying two doses of Novavax, boosted once with Novavax in the blue bar, and that's compared to three doses of Moderna in green, boosted once with Novavax, and three doses of Pfizer in gray, boosted once with Novavax. Next, we can see the IgG responses for BA.1. And finally, the IgG responses for BA.5 on the right panel. The highest antibody titers were in the Novavax homologous boosted participants, and that's true for the prototype as well as Omicron subvariant responses. However, the conference intervals are broad due to the small sample size in this group.

Overlaid here are the correlates of protection thresholds. In all cases, IgG titers achieved levels predicted to be associated with protection of approximately 88 to 95%. So overall, the 307 study findings are important because they confirm manufacturing consistency, but they also show robust immune responses to prototype and forward drift variants using homologous and heterologous boosting. The post boost titers approximate levels associated with protection in our phase three studies, however, we've seen that some of the most recent subvariants have alterations in critical conserved sequences that will impact immune responses.

So next I'd like to present data on neutralization responses for BQ.1.1 and XBB.1 for different vaccines and boosting regimens. These assays were performed at Dr. David Ho's

laboratory at Columbia University and allows for comparisons to previously published boosting regimens, including boosting with authorized bivalent vaccines. First, I'll display the anti-prototype neutralization responses derived from our studies.

I'm showing the neutralization responses in individuals who received three doses of mRNA and were boosted with our vaccine, in dark blue, compared to participants who received either four or three doses of Novavax vaccine. Consistent with what we saw previously, the homologous regimes have numerically higher responses. However, because the small numbers of participants, the precision of these estimates is relatively low. Adde now in speckled pattern are the results previously published from Dr. David Ho's lab. On the far left are three doses of mRNA boosted with bivalent mRNA vaccine, and this is displayed adjacent to three doses of mRNA boosted with Novavax. In the middle are four doses of mRNA compared to four doses of Novavax. And the right are three doses of mRNA compared to three doses of Novavax. And all these regimens provide high levels of neutralizing response.

Now let's look at BQ.1.1 neutralizing responses. Here you can see that for BQ.1.1, the responses are lower and similar across the different dosing regimens, irrespective of whether the primary series was mRNA or common protein, and irrespective of whether the boost was prototype strain recombinant protein or bivalent mRNA vaccine. The responses were suppressed compared to the prototype neutralizing responses and displayed on the left.

And finally, here's immune responses for XBB.1, and you can see even lower responses for all vaccines. Thus, whether priming with mRNA or recombinant protein, or boosting with prototype or bivalent, neutralizing responses for BQ.1.1 and XBB.1 are low. From these data, it seems that all vaccines, including our prototype booster, are performing comparably against

these variants, and all vaccines may benefit from updating to new strains to optimize neutralizing immune responses.

Now, I'd like to briefly show you the biological basis that underpins our vaccine's ability to induce broadly protective responses and also why we have diminished responses to BQ.1.1 and XBB.1. As a recombinant protein vaccine company, we make new spike proteins as new variants emerge. We've also developed a panel of neutralizing monoclonal antibodies following vaccination with our prototype strain vaccine and use these monoclonals to evaluate the structure-function relationship of emerging variants. Each of these monoclonals has been demonstrated to be neutralizing. These monoclonals also compete with polyclonal post vaccination serum, thereby confirming the relevance of this mutual evaluation. I'll show you data from three different monoclonal antibodies whose binding profile establishes the structure-function relationship.

So displayed across the top of the slide are the cryo-EM-based images, with a spike protein designated in blue and the binding of monoclonal 322.3 shown in yellow and green. This is a site two monoclonal antibody, and you can see it binds spike protein for all the variants. In the table below is the structure-function data associated with each variant, showing any mutations in the binding epitopes, as well as the ability of these monoclonals to neutralize the variant. There are no mutations in the binding region, so the monoclonals combine and neutralize.

Now we're displaying data from a different monoclonal. Monoclonal 425.6 binds conserved epitopes in the prototype strain as well as BA.2 and BA.5. Once again, no mutations occur in the binding site, and subsequently, there's no significant impact on neutralization. However, by cryo-EM, the monoclonal fails to bind both BQ.1.1 and XBB. For BQ.1.1, there's a

K4-14 mutation. And for XBB, we've identified two substitutions, the K445P, and G446S. These structural changes translate into decreased binding as well as decreased neutralization for both these variants. And finally, we're displaying the binding for monoclonal 35.13. This monoclonal is visualized binding prototype strain in BA.2, but it does not bind BA.5, BQ.1.1, and XBB. For these variants, we see mutations in the conserved epitopes, which translates into decreased neutralization. We believe changes to this region are responsible for the modest loss of neutralization we've seen for BA.5 from clinical studies.

Overall, these findings match the clinical immunology data I showed you earlier. We believe the breadth of immunity against the variants is a result of our vaccine's technology's ability to use responses to these conserved regions. When these conserved regions are altered, neutralization responses decrease. All three of these monoclonals bind and neutralize the prototype strain in BA.2 variant, signaling conservation in all three regions. The neutralizing responses against prototype and BA.2 were robust in the clinical studies.

For BA.5, as we see on this slide, binding is lost to one of the neutralizing regions, with a subsequent modest impact in neutralizing responses observed in our clinical studies. But for BQ.1.1 and XBB, there are key mutations in two of the binding regions. And consequently, the vaccine induces reduced neutralization as shown in Dr. Ho's data. The lower level neutralization response, the residual lower level neutralization response as seen in the clinic for BQ.1.1 and XBB may well be linked to the continued presence of the site two sequence recognized by the first monoclonal I showed you. So together, our structure-function studies support the current deployment of authorized vaccines but indicate that changes in the XBB lineage could be beneficial to enhanced neutralization of this and future forward drifting variants.

So in summary, our vaccine technology induces high levels of broadly neutralizing antibody and a poly functional Th1-biased CD4 cellular response. We believe the breadth of the immune response is driven by the presence of conserved functional epitopes shared amongst the variants. We've demonstrated that when our vaccine is used as homologous or heterologous boost, both as a primary boost or second boost, we generate relevant immune responses for variants and contain these conserved sequences. And that includes variants through BA.5. We have shown no additional benefit of bivalent vaccine, or variant vaccines, compared to our prototype. Valency appears to matter less in the presence of conserved sequences. And for the current vaccine composition, BA.5 and prototype strains share these neutralizing sequences. So using a monovalent vaccine until screen is selected from the new antigenic tree appears to be scientifically sound.

Finally, there's preliminary data suggesting immune responses are decreased for the most recent set of variants to the same level seen among all the vaccination regimens, irrespective of vaccine composition. Once again, this points to mutation on these conserved sequences, suggesting immune responses would be improved with more closely-matched vaccines. Our technology remains an attractive option for future annual vaccination. The breadth of immune response induced by our vaccine may future-proof the vaccine as new variants emerge.

So in conclusion, the breadth of the immune responses against future drift variants makes Novavax vaccine technology an appealing choice for future annual vaccination campaigns. Boosting data indicates comparable performance to currently available vaccines while providing an alternative to mRNA technology. Providing redundancy supply as well as a vaccine choice for the American population is a clear benefit. Novavax is prepared to deliver either monovalent or bivalent vaccine or the 2023-2024 vaccination season based on guidance from the FDA.

And our recommendation is that the regulatory bodies and manufacturers move to an influenza-like model, where strain recommendations are made by the end of the first quarter. This will allow manufacturers six months to manufacture, release, and distribute vaccines in advance of the '23 - '24 season. And we listen. We recognize the tension between selecting a strain as late as possible to increase the likelihood of recommending a matched strain versus providing adequate time to share vaccine availability. Furthermore, like it's currently done for influenza vaccines, we propose recommendations include a provision for inclusion of antigenically-like strains. As we manufacture at risk, allowing for inclusion of antigenically-like strains increases the probability of being able to provide adequate supply in a timely manner. Novavax forward to continuing to supply an additional vaccine choice for the US population. Thank you. I'll take your questions now.

Q & A

Dr. Perlman: Thank you, Dr. Dubovsky. So we have a question from Dr. Berger.

Dr. Berger: Okay. Thanks, Dr. Dubovsky, for that presentation, and I applaud the work that you and all the other companies have done to actually give this data on the currently circulating strains, as well. I have a general question. It really would be posed to all three companies at this point. It's really a question about sub-analyses and whether anything has been done to look at specifically minority populations and ensure that the performance that you're seeing isn't differentiated there.

Dr. Dubovsky:Yeah. So, so from our initial studies for the vaccine, we didn't really see that race or ethnicity was an important factor for immunogenicity. The current studies against the variants, the group sizes are really too small to be able to dig into that level of detail. Now, as we get more experience and more clinical data, we're going to be able to do those sub-analysis and certainly we have those planned as part of our ongoing.

Dr. Perlman: Thank you, Dr. Gans?

Dr. Gans: Sorry, were you all finished up?

Dr. Perlman: I think so.

Dr. Gans: Okay. Great to see you, Phil. thank you for that presentation. I may have missed it. I love the immunogenicity data that you presented to us. And I do have a question, a little bit, and maybe I'm, I'm not understanding some of the nuance to this, but I did want to ask about efficacy data. So maybe I'll just throw that out there in terms of, I didn't hear a lot of that mixed into your immunogenicity data. But on the immunogenicity question, you seem to favor a new vaccine that would be antigenically similar to what we're seeing in terms of the variants of concern that are moving. But you also show data to show that the monovalent and the bivalent are equally efficacious. So I'm not sure I — am I missing the rationale to that, then? To say that maybe it is broad enough with just some, the original monovalent?

Dr. Dubovsky:So, one thing that our data supports the, the immune responses were sound all the way through BA.5. I'll tell you, you know, the XBB is different. And we show that in the new responses from Dr. Ho's lab. Now, we've seen data today that efficacy or effectiveness is preserved even amongst these early signals for the current variants. We think that if we move to

a closer strain, we'll recover, we'll recapitulate the neutralizing responses. And so I believe that's important. I mean, I think these vaccines should be thought of not only as protecting against severe disease, but protecting against all disease, including infections. Because it's important for people not to spread the virus. It's important for people to be able to go to work and not be sick for, you know, two weeks' time every time they get an infection. So we do think that this will lead to better efficacy and effectiveness in the future, if we can move to a closer match.

Now the monovalent versus bivalent story is interesting. I mean, I lean back on the structure-function data as far as that goes. As long as we can get, you know, within, close to whatever is circulating, we believe this technology can induce broadly neutralizing responses, whether it be monovalent or bivalent. I think that we're relatively in indifferent. We can manufacture both and we can bring both to the market. And finally, about the effectiveness study. I didn't show you any, because that data is still maturing. We haven't had adequate vaccine use in places where we can capture those cases to be able to bring effectiveness data to the table today.

Dr. Perlman: Okay. Thank you. Dr. Levy.

Dr. Levy: Thank you. It's very interesting to hear about Novavax's distinct platform. A key feature of this platform is not only its use as a protein-based antigen, but the use of an adjuvant, I believe Matrix M. And so I was wondering if you might say a few words about what Novavax understands about the impact of that adjuvant on the breadth of the immune response against distinct coronavirus variants, because I think that's a topic relevant today. Thank you.

Dr. Dubovsky:Yeah. We know that the adjuvant is critical for the functionality of our vaccine. In our early studies, we tried both with and without adjuvant. And adjuvant was important for

driving neutralizing responses as well as the breadth of responses. You know, and we also know this from our influenza work, where we use Matrix M. And there, we showed in a phase three study that we generate very broad H3N2 responses, including against ancestral strains. So yes, it's critical, and I think the whole idea is that if we can get a strain selection that lands us on the same antigenic tree as what's circulating, then the value of this technology is in generating a broad response against future variants from that going forward.

Dr. Perlman: Thank you. Okay, Dr. Gellin?

Dr. Gellin: Yeah, thanks. Thanks, Phil. Just to clarify about the timing of production, you were, you were asking for an end of first quarter decision for a six-month production. Is that right?

Dr. Dubovsky:That's right. I think, very much like you see with other complex biologicals, that's the timeframe that's required for us to bring adequate vaccine to the market. Now, a couple points. I've also asked for the ability to do that antigenically matched strain, and that could certainly accelerate our timeframe. And then, just like the other sponsors, we make these things all the time. And when something new comes up, crops up, we start manufacturing. So depending on how far we all are along that manufacturing process, that timeframe could be shortened. But if you give us a strain we haven't worked on, it's a six-month time period from providing that sequence to delivering product.

Dr. Gellin: Thanks. And just one comment. So I think Pfizer raised this idea of a library of possibilities that could shorten timelines if they're available. But thank you for that.

Dr. Perlman: Okay. Thank you. I think we, well maybe we can take one more question, because we have a sharp return at 1:30 Eastern time. So Dr. Chatterjee?

Dr. Chatterjee:Thank you, Dr. Perlman. and thank you also, Dr. Dubovsky, for your presentation. I was actually going to ask the same question that Dr. Gellin asked, but the second question I have, and this may be actually to all of the manufacturing companies, is with regard to non-spike protein related antigens or mRNA. But for you specifically, does Novavax have any candidates that are more conserved epitopes perhaps?

Dr. Dubovsky:Yes. So we're focusing on the spike protein. It has been shown that neutralizing responses against the spike are protective. And, you know, as far as going for internal sequences, I mean, I suppose there could be a benefit in T-cell responses, but I'm not sure that there'd be a huge benefit from an antibody repertoire. And that's kind of what this vaccine does best.

Dr. Chatterjee:Thank you.

Dr. Perlman: Okay, thank you. I think we need to just take our lunch break now and return in 27 minutes. And the sponsors will be on the call after lunch as well, so the questions that weren't addressed or weren't asked can be asked then. So 27 minutes to 1:30, 26 minutes to 1:30 Eastern time.

Open Public Hearing

Dr. Perlman: Okay, I want to welcome everyone back, and we are going to start the open public hearing. And as we start, I have an announcement. So welcome to the open public hearing session. Please note that both the 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 sponsor's payment of expenses in connection with your participation in this meeting. Likewise, the FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. So with that, I would like to turn the meeting over to Dr. Paydar.

Dr. Paydar: Thank you, Dr. Perlman. I appreciate it. Before I begin calling on registered speakers, I would like to hand over the meeting first to Dr. Marks. Dr. Marks? Dr. Marks, you're muted. You're muted. You're still muted. Okay, what I will do is I'll go ahead and read the instructions for OPH and then I will come back to Dr. Marks a little later. I would like to add the following guidance. FDA encourages participation from all public stakeholders in its decision-making processes. Every advisory committee meeting includes an open public hearing, OPH, session, during which interested persons may present relevant information or 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. The statements made during this open public hearing session reflect the viewpoints of the individual speakers or their organizations and are not meant to indicate Agency agreement with the statements made.

I would like to try Dr. Marks one more time and see if his audio is not working and if not, then we can begin and maybe he will make a comment at the end. Dr. Marks, do you think your

audio is working right now? Thanks everyone for your patience as we're dealing with technical difficulties.

Dr. Marks: Sorry about that. That seems like the mic went on mute internally in the computer. Thanks. So, just wanted a quick announcement that FDA welcomes the expression of all views at FDA advisory committee meetings and encourages participation of interested stakeholders in its decision-making processes. FDA welcomes and respects comments related to today's meeting topic. But we don't condone comments that include offensive remarks or hate speech, especially if those are directed at members of the advisory committee or FDA staff. So I'll stop there. Thank you.

Dr. Paydar: Great. Thank you, Dr. Marks. With that guidance, I would like to begin. Every speaker will have only three minutes to make their remarks. Let's begin with our first OPH speaker, Mr. Jester Jersey. Jester, please go ahead and begin.

Mr. Jester Jersey: Thank you. I'm stating that I have no pharmaceutical conflicts to disclose. Good afternoon VRBPAC Advisory Committee and thank you for allowing me to present. Today I will talk about renewing vaccine confidence, working with community-based service organizations to increase vaccine uptake. Next slide please. I believe I'm qualified to present because I'm a member of Kiwanis International and also volunteer as a trusted messenger and ambassador with the vaccination collaborative, an effort spearheaded by Vaccinate Your Family. But today's presentation isn't about me. It's about how we can better help the American people. Next slide, please.

According to the World Health Organization, UNICEF, the Covid pandemic saw the largest decline in childhood vaccination in 30 years. Next slide, please. National Public Radio

echoed the same sentiment regarding US vaccination rates. While flu vaccine rates are low, Covid booster rates are lower at 15%. Next slide, please. How can we increase vaccination rates and trust? I'm making a motion to recommend to the advisory committee and all government health departments to work with trusted community-based service organizations, whose efforts I will present. Next slide please. I believe service groups can improve vaccination rates because of Qantas's recent global effort with UNICEF to eliminate tetanus. In 1999, 59 countries were at significant risk of tetanus. By 2019, it was reduced nearly fivefold to 13. Last year, that number was 12. Next slide please.

There's historical precedence for collaboration. Kiwanis previously worked with Nancy Reagan on the Say No to Drugs campaign during the Ronald Reagan administration. Shortly afterwards, we began our partnership with UNICEF to address Iodine Deficiency Disorder. Next slide, please. I not only advocate for working with Kiwanis, but three other organizations whose endeavors are presented before you. I recommended these groups because not only are they among the biggest service groups in the world, but they've collaborated with Kiwanis on a joint statement to address the pandemic and their breadth of experience. This includes Rotary, who are working to eradicate Polio. Next, Alliance International, who began addressing vision health after Helen Keller reached out to them in 1925. Finally, Optimist addresses childhood obesity and mental health wellness. Next slide, please. These are only a few issues to address, however many, many may benefit can be gained through collaborative efforts with service groups on any vaccine campaign, including increasing vaccine confidence. Second, reaching communities who need help the most right now. And lastly, building a foundation of trust to prepare for future health concerns, just like the Pandemic and All Hazards Preparedness Act, or PAPA, had intended. Next slide, please. Next slide.

Yeah, there's little collaboration with service organizations, particularly with trusted messaging, despite our experience with vaccine preventable diseases, this needs to change. Today I strongly appeal to an employer, members of the VRBPAC Committee, the Food and Drug Administration, the Center for Disease Control and Prevention, the Department of Health and Human Services, all other governing health departments, and even the current presidential administration of President Joe Biden, to please reach out to and connect with community-based service organizations. We can help and we can make a lifesaving difference. Next slide. Thank you. Thank you for your time and consideration. Have a nice day.

Dr. Paydar: Thank you, Jester. Next speaker is Martha Hudson, who also has a PowerPoint presentation. Please begin, Martha.

Ms. Martha Hudson: Thank you. Martha Hudson. No conflict of interest. I've used online platforms to build community for hundreds of thousands of vaccine injured around the world. Their stories are horrific. We invited Dr. Peter Hotez to join our vaccine injured Twitter spaces. His response was to block.

Until January 2021, I was healthy, traveled internationally and worked in war zones. I received one dose Moderna and had immediate reaction. My condition worsened in the first week, multiple diagnoses. Two years later, neurological and other symptoms continue. My doctors agree the vaccine is the cause. Next.

Why are we being censored? Like most injured, I've been labeled misinformation and suspended on social media for sharing factual information about my injury and others such as Maddie DeGuiere, severely injured in Pfizer's 12- to 15-year-old trial. In the current culture, it's unacceptable to discuss vaccine injuries and that tone is set by the government. This is not okay.

Twitter and Facebook internal documents show directed censorship of factual information resulting in harm to the American people. Next.

Why did it take 463 days for CDC to release critical V-Safe data? Then only thanks to ICAN FOIA of 10 million V-Safe users, which I am one. 7.7% sought medical care after vaccination. But you already knew this. Is this alarming to you? According to recent Rasmus and Po, nearly one half of Americans surveyed think Covid vaccines may have caused many unexplained deaths. Over one quarter believes someone they know may be a victim. Is this alarming to you? Three scientific problems have arisen. Virus evolving faster than vaccines. Vaccines hardwired immune response to Wuhan strain. Antibodies rapidly wane, yet you want to add these to the permanent schedule. Is this profit over people? This is alarming to Americans.

Next, why is VAERS data ignored? As of January 13th, 2023, 1.5 million adverse reports, including 33,746 deaths, have been filed. This is your tracking system. What will it take to alarm you? Recommendations, convene regional listening sessions with vaccine injured research and as researchers and doctors from all perspectives. Move VAERS out of HHS. Stop the Covid shots. At this point, there are more risks than benefits. Corporations are putting profits over people.

Next, why is the elephant ignored? The truth will be uncovered, and the level of your transparency will be judged. It is only a matter of time. Conclusion. Why did Massachusetts excess death change from respiratory to circulatory when vaccination began? See Boden v Baker. What about the massive increase in excess deaths among working aged Americans in 2021? See Ed Dows, cause unknown. Why does each dose of mRNA vaccine increase the risk of contracting Covid? See Cleveland Clinic study. We need transparency to rebuild trust in our public health system. Do what's right. Research us. Thank you.

Dr. Perlman: Great. Thank you very much, Martha, for that presentation. The next speaker is Alan McRay. I'm not sure if they made it to the room. If not, I will skip, and I may come back to this person. Alan McRay, are you present? Okay. Okay, we will move to the next speaker. I hear that he's not available. I'll come back. The next speaker is Nicole G. Nicole G.? Nicole? You might as well begin. You have a PowerPoint presentation. Nicole, are you on mute?

Ms. Nicole G.:Oh, hi. Sorry. I had some connection issues. I'm ready.

Dr. Perlman: No worries. Go ahead. Begin.

Ms. Nicole G.:Thank you. My name is Nicole. I have no conflicts of interest. This PowerPoint was created by my colleague Josh Letsgo. I am an ER nurse who worked the front lines of the pandemic. I am currently unable to work due to suffering debilitating injuries from the Pfizer vaccination, which I was mandated to receive to maintain my employment. In January 2021, the CDC released a document detailing how it is going to monitor VAERS for safety signals from Covid vaccinations. Slide two.

After first making false statements about this, the CDC finally admitted that they had done a safety signal analysis 15 months after the Covid vaccine rollout. You cannot call this informed consent, which is a legal obligation in healthcare in America. Slide three. The Epoch times recently published the results of the CDC's Safety Signals Analysis from July 2022 that they obtained from the FOIA request. The CDC said that their requests were consistent with the FDA's and revealed no unexpected signals, which can only mean that the safety signals they found were expected.

Slide four. Here is a screen screenshot from one of the CDC's Excel files. Slide five. They found 770 safety signals from mRNA Covid vaccines, two thirds of which were larger than

the signals for myocarditis. Slide six. The FDA and CDC recently announced a signal for ischemic strokes after the bivalent booster. Here are the 26 stroke signals they found from the regular Covid vaccines. Slide seven. They found many signals for a wide range of adverse event categories, including death. Why did the CDC say it was expecting these signals? 70,000 plus people isn't enough? It's enough Covid vaccine injured people to stop and reevaluate more vaccine rollouts. Enough people are suffering and dying in silence.

Slide eight. Here are the major cardiovascular signals. Slide nine. Here are the major thrombo and embolic signals. Slide 10. Here are the major neurological signals. Slide 11. Here are the major menstrual signals, slide 12. Here are the major hemorrhagic signals. Slide 13. Here are the major GI signals. Slide 14 and 15 are the worst pediatric signals found. Did you know that the FDA and CDC found all of these safety signals in VAERS? They were expecting to find these safety signals. As members of the committee, you must demand to know why the FDA and the CDC hid these safety signals and why they have failed to follow up on them. Otherwise, you'll be accomplices to more people dying, more innocent lives. Thank you.

Dr. Paydar: Thank you, Nicole. We appreciate your presentation. The next speaker is Vanessa McMahon. Vanessa, go ahead when you're ready to present.

Ms. Vanessa McMahon: Thank you. I have no conflicts. In the two years since the rollout of the Covid vaccines, there's been a dramatic increase in excess deaths in the United States. Among just the millennials, there have been more excess deaths than all the American soldiers killed during the Vietnam War. It's the same story in Australia, the UK, Canada, and all heavily vaccinated countries, and excess deaths are still rising. Disabilities are also skyrocketing, and none of this is explained by Covid infections. Countries that did not vaccinate have no excess deaths.

Slide two, why meet today? The vaccines don't work. They don't stop infection or transmission, and they were never even intended to. Even worse, the Cleveland Clinic study shows that the more vaccines you have, the greater your chances of catching Covid, and the vaccines don't prevent hospitalization or death. Slide three. Are you aware of the body of research about vaccine dangers? If not, the experts listed on slide four can help. Peter McCullough can explain how the spike protein encoded in the vaccine is distributed throughout every organ in the body, including the heart and brain, and this is after we were all assured it would stay in the arm. No one knows how long the spike stays there, nor what this will mean for the future health of vaccinated people. For this reason alone, it would be unconscionable to approve any further use of Covid vaccines. These experts also explain the sudden death syndrome that is affecting otherwise healthy young people.

The researchers and educators on slide five are another great resource. Start with Steve Kirsch, who references scores of experts in their research, including the recent Thai study, which looked into the heart issues that Pfizer and Moderna warn us about. One in four vaccinated children developed cardiac issues, often subclinical. This week, Steve looked at excess deaths and cardiac events in pilots. Naomi Wolf reports on excess miscarriages and reproductive problems, and John Campbell outlines the backpedaling that has begun in the UK, where vaccines have been banned for anyone under 50 from next month, in the light of their growing excess deaths.

Slide six has links to politicians who are calling for a stop to the vaccines. It's incomprehensible that none of this is in the mainstream media. The suppression of the data, the experts and the politicians is very organized. So stay informed by using the platforms listed on slide seven. For example, Rumble, BitChute, Substack, and Twitter, which has now reinstated

people who question the vaccines, including many doctors and scientists. Use these platforms to find Ed Dowd. Ed explains in detail the unfolding disaster of excess deaths and disabilities in the US and what this means for the economy and how Wall Street is reacting.

Finally, have you seen this week's Wall Street Journal article about the deceptive campaign for bivalent Covid boosters? Fall on Robert Kennedy, Eagle Chewdoff, and Ted Victory. They all have a wealth of knowledge on the tactics used to influence clinical trial outcomes. Thank you.

Dr. Paydar: Great. Thank you, Ms. McMahon.

Ms. McMahon: I can see that the slides didn't keep up with me.

Dr. Paydar: Yes, they did not. We will have them on the record, and also, they will be saved when it's transcription. That was unfortunate, but they are captured for sure. Rest assured.

Ms. McMahon: Would you mind just going back to slide seven for a second, just so that we can make sure that the platforms are shown there? The rumble, the BitChute, and the Substack, and Twitter?

Dr. Paydar: Sure. Is this the slide you're referring to? Can you see the slides on the screen? Data driven answers and evidence.

Ms. McMahon: Not that one. The next, the next one. And go to the next. Please go on to the next one. It’s just important, so that people can access.

Dr. Paydar: Yes, it will definitely be on their record. It's this all okay. It is recorded that can access so people can definitely access.

Ms. McMahon: It's just important —

Dr. Paydar: And it's also transcribed and definitely saved on YouTube. And it's also saved, so rest assured it will reach everyone. It's recorded. No problem. No worries.

Ms. McMahon: Thank you.

Dr. Paydar: Thank you for your presentation. Next person is Dr. Robert Edmonds. Please go ahead, Robert.

Dr. Robert Edmonds: Dear committee. I address you as an admin of a tinnitus adverse event support forum. My only conflict is the unlikely copay reimbursement in the $2,000 range from CSUN by work to influence recognition and later file a claim. With that, my comments as a triple, but unfortunately not quadruple, dosed individual are not being made to dissuade vaccination, but have the goal of further improving frequency and outcomes for an unlikely event. That is tinnitus after Covid vaccination, which I developed nearly two years to this day after my dose one. My wife would also later develop tinnitus in mid-March of the same year, in line with her later phase access and dosing. We still hear our rings as I speak to you.

This is an important distinction. This is unlike some other adverse events that resolve, but also it is also so intrusive. We have regularly provided suicide hotline information in our groups. This issue though, is informed to this committee, a prior member and editor in chief of vaccine, Dr. Cohen, also developed tinnitus along with his wife. He also experienced variability to his ring after being rechallenged. While many others along with myself didn't develop tinnitus after Janssen, I thought it would be best to spotlight it in a slide here, because it has a particularly strong argument for tinnitus being related, but is still not recognized in the US.

Both passive monitoring signals mentioned in the slide were observed for Janssen, but I highlight the second because it has not yet been reported. This is because I followed up with Dr. Harpaz at Oracle Health Sciences and his group, which includes FDA co-authors, that report in drug safey, the effective masking and pharmaco vigilance speak on signals and VAs data.

The group didn't consider to examine Janssen, but after requested re-analysis, they identified a prior mass signal for tinnitus for this vaccine, the orange curve and the figure. The blue represents a much lower signal score, like what is probably produced by the FDA. So I ask, how much longer do the vaccinated, not the anti-vax, those that develop tinnitus after Janssen have to wait for the FDA to account for masking within their monitoring? Or has this already been accounted for? And after all the imbalances, the passive monitoring signals, the foreign government recognition, and recognition for a vaccine of the same platform, that this is still actually not enough for recognition here.

If this is the case, where's the funding for EHR database or inner ear tissue analysis papers that researchers like Dr. Harpaz or otolaryngologist Dr. Stankevich at Sanford want to do? I want you to find answers to these questions. That's my call of action to you. And this just scratches the surface for the challenges of recognition or work of with just one vaccine that may be the key to your future peace and quiet. So please don't make your response the same that Dr. Thompson Bankura had when I asked for research, which was quote, thank him for his email, cut him off. We were cut off, but we are still here. Thank you for your time.

Dr. Paydar: Thank you for your presentation. I appreciate your time and presentation. The next speaker is Dustin Bryce, interest of Justice, also a PowerPoint presentation. Go ahead Dustin.

Mr. Dustin Bryce: Hello, my name is Dustin Bryce, interest of justice.org, and we have zero conflicts of interest. This first slide shows why FDA has no reasonable belief the unproven intervention may be effective and why it's not proven safe. FDA has no choice but to revoke the EUA and stop the experimental shots today. It needs to be stopped today. The FDA asked for 75 years to hide Pfizer trial data, which showed 1,223 confidential and proprietary deaths in the first three months. The same documents when the court ordered not only showed piles of dead bodies from Pfizer trial, but the signals of enhanced disease, and showed that enhanced diseases an identified potential risk not in the EUA fact sheet. The phase four data shows death is common and the number six effect after 30 days of taking Pfizer BioNTech. Next slide, please.

The whole thing is not allowed under the WHO MEURI ethical framework, which guides FDA on a strictly exceptional basis. It may be ethically permissible to use an unproven intervention outside clinical trials, but only if the monitored emergency use meets the rigorous ethical criteria spelled out by the MEURI ethical framework, which the Covid vaccine regimen does not meet the ethical criteria, thus making it mandatory to stop the shots now. A quote from the framework proves the EOA factsheet omits what is required for informed consent, making the exceptional EUA completely prohibited. In quotes, A consent process for use of unproven clinical interventions that does not explicitly recognize the scientific community's uncertainty about the risk of benefit to about the risk benefit to ratio is not ethically appropriate. End quotes.

The FDA's not considering community engagement with experts who dissent, and that's a big problem for the future regimen of the EUAs. We would like to read to you verbatim, in quotes, widespread use of the unproven interventions outside clinical trials for the in preventative interventions should therefore be discouraged, as all harm related to the interventions is

iatrogenic. Iatrogenic means introduced by a physician, such as a complication resulting from the treatment, and it's a real possibility, and it can happen. Next slide, please.

The FDA's omissions explicitly recognize and inform the public about the scientific community's uncertainty about the risk benefit profile threatens the validity of informed consent and community engagement, which are required under the ethical framework and make the COVID-19 non-vaccine prohibited. This is a huge problem. That is why the future of Covid vaccines should be prohibited and is prohibited by ethical standards, including Nuremberg code. Let us remember, in quotes, unproven intervention means lack of sufficient evidence and includes the term experimental. FDA is authorizing human experiments in a way that violates ethical boundaries and not adequately monitored the potential risk of enhanced disease. Which is why the EUAs must be revoked immediately.

Community engagement is essential to establish and maintain trust and preserve social order. Comment on our citizens petition now. The evidence is in our petition, and if you want to stop the shots, go to our Amended Citizens petition and comment. It's FDA dash 2022 p dash 24 11. Share it far and wide. Go to go to the FDA website and go share it far and wide. Thank you so much.

Dr. Paydar: Thank you for your presentation. The next speaker is Dr. Arun Upadhyay, Chief Scientific Officer, Ocugen. It's also a PowerPoint presentation. Thank you.

Dr. Arun Upadhyay: Thank you. Good afternoon. Thank you to FDA for giving us opportunity to speak at this meeting. My name is Arun Upadhyay and I'm Chief Scientific Officer at Ocugen. There are several at risk cohort in the US where sequential or even concomitant SARS-CoV-2 and influenza infection can result in increased digit severity, morbidity and mortality. This

emphasizes the urgency for developing a novel mucosal combination vaccine against COVID-19 and influenza. Today we are excited to say an overview of the first mucosal COVID-19 and signal flu combination vaccine, which is in the development in the US and designed to be delivered by inhalation. Our goal is to address a significant gap in today's Covid and flu vaccines, specifically the need to establish local mucosal immunity in respiratory tract while also preventing digits, morbidity, and mortality. Our vaccine candidate will use prevent technology to achieve this. Next slide please.

The platform technology for our vaccine. Eli Noel Chad 80 36, no Sector. It was developed by Washington University in St. Louis and has been demonstrated as safe and effective by behalf Biotech India following Nigel Drop dropper administration. In addition, consign in China has developed a similar vaccine featuring a human 85 vector. But in contrast it has an ENT route of administration. Ocugen utilize is the non-human derived child, 80 36 vector with an inhalant-based delivery technology in the United States. This approach has potential to gender broad immune protection against COVID-19 incisal flu with an excellent septic profiling profile by using a significantly lower dose compared to intramuscularly administered EDNO vector vaccine. Next slide.

We intend to initiate the first clinical study of the COVID-19 inhaled vaccine in later part of this year. We could have a combination in inhaled COVID-19 and signal flu vaccine ready for huge ASAP by working closely with the regulators. Next slide, please. The mucosal combination vaccine will be inhaled from a cup. This vaccine will be simple, needle free, pain free, easily administered, safe, effective, and will utilize a marketed and validated nebulizer device, which dispenses a mist into a disposable cup to prevent any cross-contamination. The manufacturing

platform technology will be easily adaptable and scalable, to signal variants or emerging variant of concern or flu and SARS-CoV-2 virus respectively. Next slide.

In summary, Ocugen plans to develop an adolescent based COVID-19 flu vaccine that has efficacy against hospitalization, severe cases, symptomatic cases, and asymptomatic cases. For this, we'll be developing three inhalation vaccines using the same platform and inhalation route, using COVID-19 vaccine, flu vaccine, and the combination of both. We'll be seeking Agency feedback on the development plan in the US. Thank you for your time.

Dr. Paydar: Thank you Aaron. this is the end of the PowerPoint presenter's session, and we will now begin with the next eight presenters who will only make their comments orally. I will begin with Danielle Baker.

Ms. Danielle Baker: I am Danielle Baker, and I have no conflict of interest. Hear me. The vaccine injured are real. In June of 2021, I reluctantly received the Pfizer injection after being coerced by my former employer. I had a 17 year career as a certified and hospice palliative care registered nurse that I loved and was part of my identity. I had a fall within 12 hours of receiving the second injection. 24 hours later, my symptoms progressed, and I sought care at the ER. Agonizing pain in my right injected arm, it radiated into my face, causing me to scream out in pain. This was a direct result of the injection, but because of the safe and effective narrative, I didn't get the care that I needed, and I was dismissed within 30 minutes without answers.

By the end of July, I was hospitalized, unable to readily walk, muscle spasms contorting my body, and constant excruciating pain, and the humiliation of losing my bowel and bladder function. My immune system attacked my spinal cord, and I was diagnosed with transverse myelitis. My physician documented this as a direct result of the shot. My family is unable to plan

events, because I don't know what I can tolerate each day. Will this spam be so bad I can't even rest in bed, or will I be in such unbearable pain I can't have you in touch? Even speaking is hard because of the damage done. I unwillingly traded being a caregiver for medical equipment receiving care in bed sores.

We are in financial ruins because ironically, I took the shot to keep the career that I loved and I no longer have. I submitted a VAERS report as well as a MedWatch on August 4th, 2021. My VAERS report disappeared from the system, and I heard nothing from the FDA. Is it because you take your marching orders from Pfizer or Big Pharma? Will you continue to pretend I, we, the vaccine injured don't exist? The only thing we're humiliating that, listen, my bodily function is your complete disregard for the vaccine injured. Shame on every single one of you. My former employer doesn't care. My CDC doesn't care, and it seems my FDA certainly doesn't care.

Dr. Paydar: Thank you Danielle, for sharing your experiences with us. I'm truly sorry to hear of all the pain you've had to endure. I, again, appreciate your participation. I can't thank you enough for taking time to share it with us. Thank you very much. The next speaker is Tim Dowling.

Mr. Tim Dowling: Hello. I have no pharmaceutical conflict of interest. Messenger RNA vaccines were first researched as the therapeutic platform for the treatment of cancer. No such option was offered to my father when he was dying of prostate cancer three years ago. I do speculate that this is because the profit margin for developing it was low. However, the proof of the pudding is in the eating.

By now, it is ludicrously obvious that we all know people who are worse off since receiving a Covid vaccine. A WhatsApp group I belong to from Choco Colombia has seen 10

sudden deaths of young people since the rollout started. There were none for three years previously. In other places, friends and their friends, include a woman with no previous history of cancer, who developed complex colon cancer following her first shot and was dead in weeks. A fit woman in her seventies, dead of a stroke. A close friend of my sister's husband, always in good health, a cycler and hiker, since his shot, he is immunologically suppressed with frequent colds. A Colombian friend of mine, an author, who developed high cholesterol and a heart condition. Previously fit, my sister, the matron of an emergency board, has had Covid four times, despite being vaccinated with all boosters. My brother's wife's asthma shot into action following her shots. My sister-in-law and her husband developed respectively menstrual disorders and skin cancer after receiving Pfizer. A man of 65 collapsed and died in front of my wife and son following a shot. I grew up in a medical family.

I have never seen anything like this before. I put it to you that no one has statisticians employed by parties with declared or undeclared interests to defend will accuse me of advancing anecdotal evidence. I will accuse them of crying all the way to the bank. Ladies and gentlemen, do you have hearts of stone? However, shockingly, none of this is any surprise. Catalin Carto, in her 2015 study funded by Bill and Melinda Gates, records that I quote, a large portion of the Lucifer Rays activity was detectable in the liver. End quote.

And back in 2014 before Soviet style Bravada prevailed in our world, Kyle Fu et al note in their research, colloidal instability in biological fluid is a poorly understood phenomenon. Particle aggregation can be caused by interaction between the cat nanoparticles and the components in blood. When injected into the systemic circulation, positively charged nucleic acid nanoparticles aggregate through interaction with erythrocytes and other negatively charged sera proteins, such as albumin. Unquote. And they quote Ho et al, who also say the shots cause

clots. Messenger RNA is a promising platform, but it is time to stop and recapacitate. The bad faith and profiteering has been such that the principle should be extended across the smorgasbord of vaccines. This is our fellow human being.

Dr. Paydar: Mr. Dowling, you're over your time. Please conclude.

Mr. Dowling: This is our fellow human beings we are talking about. Our species. Ladies and gentlemen, stop the rollout.

Dr. Paydar: Thank you. Thank you for sharing your presentation. the next speaker is Nicola Adolphe. Please go ahead.

Ms. Nicola Adolphe: Thank you. Nothing to declare. Hello everyone. I'm very pleased to be here. I run the Autonomy Hotline in the UK. Our organization is an advocacy service, helping to support people's rights in health and social care. We are passionate about informed consent, the gold standard in medical practice. For the vulnerable who cannot consent to treatment, children, elderly, disabled, there is a danger that medical practice becomes what we do not want it to become. When authorities discuss licensing vaccines, they emphasize reaching the most vulnerable members of society with these products. But the truth is, society has no problem coercing vulnerable groups of people to line up first. Their bodies are not their own.

For example, writing a vaccine order in the family court leaves families penniless or fleeing their homes. In mental health hospitals, vaccines are disguised as treatment, which is illegal. A family member saying no to the vaccine on behalf of an elderly relative loses their power of attorney. The Down syndrome teenager living at home, a court ordered vaccine could mean the use of police powers to gain entry. The autistic adolescent, sedated and restrained by

court order, to be given something he said he didn't want. Where are the disability rights that society claims to uphold?

For all you here today, because you are vaccine injured, this is just the tip of the iceberg. Everyone is so keen to seize any form of consent that the precautionary principle doesn't appear to apply outside of the patient-professional relationship. If a decision goes to court, the courts will simply authorize the vaccine with no regard for the ethical implications involved. The FDA committee must recognize that you open a door to a slippery slope that the rest of the world seems keen to hurdle down. The availability and licensing of vaccines paves the way for professionals to abuse their power over those on whom the benefits cannot be proven.

Some of the worst violations of human rights were done in secret in the name of vaccination, but at the expense of sound medical practice. It is one global Milgram experiment. The very people you license this product for will be coerced by those in medicine, social care and law, dividing families and causing harm. When this happens, there's no best interest outcome. There's no greater good. As a Christian, I'm called to take a stand for these individuals, and I say in the name of Jesus, this injustice needs to stop. Before any vaccine is released, you should ensure they're only given to people with capacity to consent, with full disclosure of risks, and any no should be as welcome as any yes, without fear of penalty or court appearance. Thank you. Please support the Autonomy Hotline.

Dr. Paydar: Thank you very much for your presentation.

Ms. Adolphe: Thank you.

Dr. Paydar: The next presenter is Justin Prince.

Mr. Justin Prince: Hello, my name is Justin Prince. June 22nd, 2021. Moderna shattered my life. Upon receiving the shot, my face went numb. I had a metallic taste in my mouth, and I felt like I was going to pass out. The following morning, I woke up with extreme chest pains, a heart rate of 144, and numbness in my body. I went to the ER four times within a month. They attributed my symptoms to Covid, despite the fact I never had Covid. I quickly found myself in many doctor's appointments in an attempt to alleviate my symptoms, such as extreme chest pain, tachycardia, bradycardia, widespread muscle and joint pains, extreme paresthesia, tinnitus, headaches, newly acquired food allergies, and becoming immunocompromised. And that's just to name a few.

I've seen doctors in nearly every specialty field that echo the same phrase. It's an adverse reaction. Ride it out. This is a failure to identify condition caused by this vaccine and receive early treatment to prevent it from progressing. Our doctors follow government protocol on how to treat Covid. There's long Covid clinics in every state. Why are there no studies on adverse events, treatment protocols, vaccine injury clinics, or long-term safety studies? The injured are left to their own devices without any compensation because you are more concerned with managing a safety narrative over acknowledging these vaccines are a problem.

It's a breach of the Hippocratic oath of do no harm by forcing mRNA vaccines on children who are low risk of Covid complications and a higher risk of developing adverse reactions from the vaccine. This defies logic and only makes sense in the context that the FDA received a large percentage of its funding from the pharmaceutical companies it's supposed to be regulating. No one who got the shot gave informed consent, because the risks were censored, and the benefits were falsified. Every shot was unethical and a medical malpractice. Before the vaccine, I was a healthy musician, able to work with my hands without limitation. Now at 29, I

cannot pursue my passion without being in pain or even work a full-time job. I tested false positive for HIV six times over 103 days, which my doctor determined was a direct result from the vaccine. I've been to the ER 14 times, and more doctors' visits since the shot than my entire life combined.

I'm an empty shell of my former self, and I often wish the vaccine took me out the day I received it, as opposed to having zero quality life and struggling to survive, because the government doesn't compensate for vaccine damages or fund studies to treat them. I no longer have any dreams to pursue. My only objective is just trying to stay alive and endure these vaccine damages. I encourage you to hear our cries for help as if we were family. Would you still abandon us then? Thank you.

Dr. Paydar: Thank you, Justin. Thank you for sharing your personal experience with us. We very much appreciate it. I'm sorry to hear of your pain. The next speaker is Angie Bluford. Angie, please go ahead.

Ms. Angie Bluford: Thank you. I have no conflict of interest. My name is Angie Wyatt Bluford, a 49-year-old mom of two living in Wilmington, North Carolina. The beginning of 2021, I was in the best shape of my life, enjoying power tools, projects, and food. My husband and I just completed our chicken village and were wrapping up our critter proof garden. On April 15th, 2021, I gladly took my second Moderna vaccine to protect my family. My life has not been the same since.

The next morning, I woke up in a lead suit that gets heavier depending on weather, what I've done, or just for the hell of it. The migraines, excruciating head pressure, and bone pain robbed me of the smile that once graced my face, along with the shortness of breath, fatigue and

cognitive issues, I'm forced to take my second leave of absence from work in 13 months, I've been denied short-term disability, taken loans from our 401k, withdrawals from life insurance policy, and racked up tens of thousands of dollars in medical bills. Managing my symptoms has affected my ability to be a great mom, wife, and employee. My body is a shell of what it once was, and my mind not far behind.

Imagine waking up every day not knowing what your body can or cannot do, and it's all because you thought you were doing the right thing. Per the CDC's website as of yesterday, and I quote, the mRNA from the vaccines is broken down within a few days after the vaccination and discarded from the body. End quote. I have test results showing the spike protein was still present and wreaking havoc in my body 603 days after my last Moderna vaccine. And I've never had Covid. No words can articulate the physical and mental anguish endured in almost two years. Yet I'm a fortunate one. I'm alive. I'm fighting my fight, along with other far more injured. To ensure no more lives are impacted or lost, please hear us and help us.

There should be an extension from one year to three years to file claims through the CICP. The suppression of data and gaslighting prevents those impacted from finding doctors to listen. In addition, I ask you to immediately stop administering vaccines until further research is completed and the public has true informed consent. Thank you.

Dr. Paydar: Sorry, I was on mute. Angie, thank you so much for sharing your stories. I can understand how difficult it is to share such personal experiences. Our prayers are with you, and thank you for your presentation. The next speaker is Kerri O'Neill. Kerri, please go ahead.

Ms. Kerri O'Neill: Good afternoon. My name is Carrie O'Neill and I have no disclosures. I am not anti-vax. I felt that being vaccinated for COVID-19 was the right thing to do. This said,

in order to make an educated choice about receiving a vaccine, every person deserves to know the actual risks. In December 2021, 12 hours after receiving the Moderna booster, I began experiencing severe gastrointestinal issues lasting two weeks. 10 days in, while driving, I became tachycardic and dizzy. My head, neck, arms, hands, and body began tingling. My hands were clamping closed, and I was having difficulty breathing. I ended up in the ER, with face and arms still tingling, arms jumping involuntarily out of my hospital bed, abnormal echoes and EKGs, and very low blood pressure. I was admitted to the hospital after much testing. Over the next 24 hours, I was released with no definitive diagnosis, except that maybe, considering the timeline, I was having a reaction to the booster. I felt horrible and I knew something wasn't right. This was the first of five ER trips, two hospital stays, and a cascade of doctor and specialist visits, with symptoms multiplying by the day.

It was affirmed I was having a severe reaction to the Moderna booster. I soon had a team of specialists in cardiology, neurology, rheumatology, gastroenterology, hematology, immunology, infectious disease, and POTS, who were all treating patients suffering from Covid vaccine injury. Each are considered top in their field in Los Angeles, California, and their practices span across Cedar Sinai, UCLA, and St. John's hospitals. They surmise the Covid vaccine can trigger the autonomic nervous system, which can lasso in just about every other system in the body. My symptoms list goes like this: disautonomia to include nausea, tachycardia, arrhythmia, pericardial effusion, cardiac edema, chest pain, dizziness, neuropathies, fasciculations, pulsatile and tonal, tinnitus, internal jolts and vibrations, adrenaline dumps, a blood clot, low blood pressure, burning eyes, sinus pressure, inappetence, severe pain in my neck, back, torso, hips, legs, joints, bones and Achilles tendons, and with all of it, anxiety.

For four months, I was too dizzy to drive and spent the lion's share of my days resting at home. This meant not being able to take my daughter to school or attend her ski races. It meant not being the mom that she was accustomed to. I was blessed to have her father, our friends, and my family to take up this sudden slack. I was accepted into cardiac rehab at Cedar Sinai, and as a healthy 50-year-old lifelong athlete now on beta blockers, was eventually able to ride a stationary bike alongside heart surgery patients in their eighties. This therapeutic body work, my naturopathic doctor, and the support of several people in the same boat have been godsends in supporting my recovery. I still awake not knowing what symptoms will be lurking. They continue to come in waves, and while many have waned, several linger and affect my day-to-day living, I worry about what lasting damage has been done to my body.

My specialist state, the number of people experiencing vaccine side effects is larger than is reported, and symptoms ranging from mild to catastrophic are not rare. Covid vaccine injury symptoms are straightforward and at this point should raise a bright red flag to doctors in their diagnoses. It is well past time to acknowledge these risks.

Dr. Paydar: Kerri, I'm so sorry to cut off. We need to give other people a chance to speak. Are you ready to conclude your remarks?

Ms. O'Neill: Yes. My neurologist believes it is the tincture of time that will allow our bodies to heal from Covid vaccine injuries 14 months out. I am hoping she's right. Thank you for your time.

Dr. Paydar: Thank you. I'm so sorry to hear of all your personal experiences. My prayers with you. Thank you so much for taking time to share with us. The next speaker is Russell Milko. Russell, please go ahead.

Mr. Russell Milko: Good afternoon. My name is Russell Milko. I have no disclosures. As a former manager for a major pharmaceutical company, I represented several drugs, including injectable vaccines. The vaccines I represented took over 20 years to receive FDA approval after double blind, peer reviewed studies. The guidelines for approval were very strict and closely monitored to ensure the efficacy and safety of the vaccines. This is what we have come to expect from every single drug that is released for use.

None of these protocols have been applied to these gene therapy drugs. Will this committee be willing to look at a new peer-reviewed study that shows 217,000 were killed by the Covid gene therapy products in the first year of use? By definition, as we all know, these products are not vaccines. They are experimental gene therapies. The peer reviewed article by Mark Skidmore is entitled The Role of Social Circle COVID-19 Illness and Vaccination Experiences, an Online Survey of the United States Population. Mr. Skidmore used survey data and ratios of vaccine deaths to COVID-19 deaths that suggest that the number of fatalities of these gene therapy products may be as high as 278,000 people.

Nobody wants to talk about it because that's the way science is. And it works, right? Most likely, Mr. Skidmore's paper will be retracted. Did the FDA do any surveys of the population like Mark Skidmore. If they did, we all would like to see the data. Is the FDA not doing any surveys on the population because they are afraid of the results? As I interact with doctors all over the country that have taken these Covid shots, they have expressed regret in taking them. They had no choice at the time, because they were forced to take the shots or lose their hospital privileges. I ask the FDA advisory committee to have a private session with Doctors Peter McCullough, Robert Malone, Asim Malhotra, Pierre Corey, and someone who has taken many of these

surveys, Mr. Steve Kirsch. Furthermore, these gene therapies need to be taken off the market like Dr. Al Malhotra has asked the authorities to do in Great Britain. Thank you for your time.

Dr. Paydar: Thank you, Russell. I appreciate your timing. The next speaker is Terry Jenkins.

Ms. Terry Jenkins: Hi. Yep. I have no, what do you call it, conflicts of interest. I own a small business and I've always stayed very active. Prior to the Pfizer vaccine, I worked out five to six days a week, and the only health issues I had was scoliosis. When I got my first Pfizer dose on July 22nd, 2021, when I got the shot, I immediately tasted metal. Within a couple of minutes, my throat began to feel tight, but I chalked it up to nerves. A couple hours after the shot, I began feeling sick. I was short of breath. My chest felt tight, and as the hours went on, I began feeling tired, and I thought this was all normal. At 9:30 at night, I began having a pain in my right calf, and I also had tingling in my hands and my feet. I was concerned, but I told myself it can't be related.

I gaslit myself. No way was this the vaccine, because it was said to be safe. The next day I had new symptoms, nausea, headache, racing, heart coughing, diarrhea, and I became very sensitive to light. That evening around 9:30, I lost all the blood in my fingers from the second knuckle up. They had gone completely numb and cold. Same with my toes. I knew that wasn't normal. It wasn't in my head. I saw my doctor July 25th, and she told me I had an anaphylactic-type reaction and not to take anymore and dismissed the rest of my symptoms and sent me home. The next day, I had multiple mini strokes. Over the next weeks, the tingling that I had turned to numbness, burning, and freezing. I was diagnosed with small fiber neuropathy, peripheral neuropathy, Reynard's phenomena, paresthesia, and I have autoimmune issues now. I have brain fog, headaches, and tinnitus. My doctors have both said this was the Pfizer vaccine, but they did not know how to help me.

The only medication that worked is ivermectin. It got rid of my light sensitivity, my headaches, and my brain fog. I can no longer work full-time due to my health. I have permanent nerve damage, and there is no way to seek financial compensation for this. This is a crime against humanity. My family misses me, and I miss me. Why were the people in the trial injured and you never reported it to the public? Why do people and families have multiple people in their family that have been affected by this vaccine? My father had blood coming out of his ears after his fourth shot. He died of a subdermal hematoma. Three months later, my government has failed so many of us. You have gaslit with us. You have made the public think we are liars. We are under attack right now. We have articles being written about. You guys did this and you need to come up with a solution. Please stop these shots before they hurt anybody else. At least warn people that the adverse reactions that are happening. People actually think their people aren't dying and being hurt.

One last thing. How ethical is it to move board members from the FDA to the CDC to the pharmaceutical companies? You can save your breath, because I can answer it. It's not ethical at all. How many more people have to die and be injured for you to stop this shot? How do you sleep with yourselves at night knowing that people are dying and being injured? Please search your souls, for, because this is going to be a very, very bad year. This died-suddenly are continuing to pile up, and this needs to be investigated. Please stop these shots. Thank you.

Dr. Paydar: Thank you, Terry, for sharing your personal stories. I'm so sorry. Thank you so much for taking time to participate. Our last speaker is Allan MacRae, and he will have a PowerPoint presentation. Alan, we're coming back to you. Let me know when you're ready for the presentation. Go ahead, for three minutes. Yes, go ahead.

Mr. Allan MacRae: I'm ready. Could I have my first and second slide please? Let's go to the second slide. Covid chronology. I studied COVID-19 full-time for three years since January 2020. In February 2020, I identified the pandemic as a scam based on credible foreign data. More on that later. On the 20th of March, I learned that our Alberta hospitals were empty, and I decided to publish. The anticipated flood of Covid cases never showed up. On the 21st of March, I published the lockdowns were not justified and would be net harmful. That's almost three years ago. On the 4th of October, world experts published identical conclusions in their great Barrington Declaration. On the 8th of January 2021, I advised my governments to not release the dangerous, toxic COVID-19 injections. That's over two years ago now.

Why was this COVID-19 pandemic a scam? The data showed that the virus was only fatal to very elderly and infirm, not to younger people. There were no excess deaths in Alberta or Canada in the 12 months ending mid-year 2020. None. The hype was identical to the climate scam, which was completely disproved in 1990 and several times later. The same usual suspect promoted both the climate and Covid scams and linked them together saying to solve one, we have to solve the other. Absolute nonsense. There were so many scientific irregularities in this process. PCR tests were overrun to create many false positives. The so-called casedemic. Ivermectin was banned, a criminal act. The vaccines actually drove the variants. Basic Darwin. Both the COVID-19 lockdowns and the vaccines were ineffective, hugely harmful, and too often fatal. Next steps to fix, to stop this disaster. Stop all COVID-19 injections immediately. Do no more harm. Make available the best medical treatment to reduce harm to the vax.

Finally, and most importantly, make inexpensive voluntary, over the counter ivermectin plus packages widely available for treatment of the Covid illness and the vax injured. This is the most important thing I have to say. We really have to try and save lives. We have the opportunity

to save thousands or even millions of lives by taking some remedial action now. That is all I have to say. Thank you very much.

Dr. Paydar: Thank you, Alan. I appreciate you being on time. This concludes our open public hearing session for today. I would now like to hand over the meeting back to our chair, Dr. Perlman. Dr. Perlman, you can begin with the next section. Thank you.

FDA Presentation

Dr. Perlman: Thank you, Dr. Paydar. So the next part of the meeting is going to be uh a talk by Dr. Jerry Weir, the Director of the Division of Viral Products, who's going to tell us about potential changes to COVID-19 strain vaccine strain composition.

FDA Considerations for Potential Changes to COVID-19 Vaccine Strain Composition

Dr. Weir: Thank you, Dr. Perlman. We've all heard a lot of data and a lot of presentations already today. What I'm going to do is go over a lot of what we've already heard, but not in that sort of detail, but to try to make a few key points to lead us into the discussion items and the voting question that will follow in the committee discussion of those items. Next slide.

We'll start with some background. At a previous meeting on April 6th, 2022 of the Vaccines and Related Biological Products Advisory Committee, the committee had an initial discussion about the process that would be used to update the strain composition of COVID-19

vaccines in the US and considerations for the use of additional booster doses. In a later meeting on June 28th, 2022, the committee discussed whether and how the SARS-CoV-2 strain composition of COVID-19 vaccines should be modified. At that June 28th, 2022 meeting, the VRBPAC voted in favor of including SARS-CoV-2 Omicron component for Covid-19 vaccine booster doses in the US.

There was a general preference at that meeting for a bivalent vaccine containing the ancestral, or Wuhan, and an Omicron strain. A couple of days later on June 30th, the FDA notified vaccine manufacturers of their recommendation to develop a bivalent vaccine that included the ancestral strain plus an Omicron BA.4/BA.5, and to use this as a booster dose to improve protection. The first bivalent vaccines from Moderna and Pfizer BioNTech were authorized for youth of 18 years and older and 12 years and older, respectively, on August 31st, 2022. At the time of that meeting in June, there was no change in the composition recommended for the primary series vaccines. I'll come back to this a little bit later.

What I want to do now is touch on several different topics that we've gone through during the day. The next slide will go to a little bit of epidemiology. The next slide. SARS-CoV-2 Virus epidemiology suggests continued evolution and spread of virus variants. Next slide. The next slide shows the phylogenetic relationship SARS-CoV-2 variants. I like showing this because it's a very simplified version of how the virus has evolved. It comes from a website, covariants.org, at the bottom, using next strain data. But the key messages from this are that everything changed with the appearance of Omicron. For those of you that aren't too tired of the influenza analogies, in a sense, Omicron was more like an antigenic shift and an antigenic drift. And since that time, everything has evolved from Omicron. In fact, it's more specific than that. Pretty much everything has evolved and derived from a BA.2 version of Omicron. Some of the most recent

variants like the BQ viruses have actually evolved from BA.4/5, and even the more recent XBB strains are actually recombinants from other BA.2 viruses, like BA.2 10.1 and BA.2 75. The next slide.

I've got two slides showing what you've already seen today, and that's how the variants have continued to evolve and spread. This one comes from, also comes from Covariants, and it shows the entire course of the pandemic. And you see in the color coded the different variants on the right. What happened after our recommendation, it's pretty clear that BA.5 and it's, and the BQ viruses dominated for several months actually, but now they're gradually being replaced. And this is the US with the XBB strains. The other nice thing about this website, of course, is it's not just US-centric. You can click on any country and see what the circulating variants are in that country. Oh, the next slide shows one that you have already seen. This is the one comes from CDC, slightly different methodologies, but the message is the same. the virus continues to evolve. The XBBs now are increasing and in numbers compared to the other strains. And as these viruses continue to evolve, we have to adapt as well.

So what do we know now about the performance of what we recommended back in June? To go to the next few slides and talk about some data at a very high level of what you've already seen. I think you skipped one, but that's okay. Immunogenicity data indicate that the recommended bivalent booster vaccines elicit improved variant specific neutralizing antibody titers. The next two slides are really high level of what you've already seen. I separated in the by, in this slide data from the manufacturers, and you've already been presented with this during the day. On the left is Moderna data. On the right is Pfizer data. I want to make a couple of points about this though. These studies, the ones from Moderna and Pfizer, are prospectively designed studies. They were submitted to the Agency for review. They contained large enough numbers

that we could get statistically significant data from them. But really importantly is the assays used for evaluating these trials are qualified, in most cases validated. But they're subject, they have been subject to much back and forth with the Agency so that we can be confident in the results that we get. But the take home message is pretty clear, and that is that in both cases, the updated vaccines improve the variant-specific neutralizing antibody titers.

If you go to the next slide, this is some, some additional data. results have recently been reported from several other studies that describe the neutralizing antibody responses to these vaccines that we recommended, the vaccines that contain an Omicron BA.4/BA.5. There are a couple of caveats to remember about these. One is that the main thing is that the interpretation of data from these studies is complicated by several factors, including the limited number of subjects, differences in sub-study populations, intervals between vaccination and sera collection, and importantly, the variability in the type of assays used as well as in the status of assay qualification. None of this data has been or probably will be submitted to the FDA, and the FDA doesn't actually make a determination about the scientific or regulatory applicability. But nevertheless, the results from all of these currently reported studies, and I've listed several at the bottom of the slide, they're in the briefing document, but most people have seen them.

The important thing is that the results all trend in the same direction. In other words, with all of these studies, just like those from the manufacturer, there is an improved variant-specific neutralization following administration of the bivalent BA.4/5 vaccine compared to a monovalent without an Omicron component. In a couple of cases, the authors concluded that the differences weren't significant, and a couple of other cases they said they were, but the important thing to remember is how uniform the data is. That it all trends in the same direction. And

actually, I find it somewhat remarkable to see that level of uniformity among all of these studies, as well as those from the manufacturer.

So the next few slides, I want to move on to what we know about the observational effectiveness data. And here now at this point in time, we have observational effectiveness data that provides real world evidence that supports the use of the recommended bivalent booster vaccine. The next slide gives a quick summary of this. Results have been reported now from several observational studies of recently recommended booster vaccines containing the BA.4/BA.5 component. These studies differ in their design. Each has some limitation, and I only mentioned that to point out that with observational studies, there's always some limitations to them. They're never quite the same as prospectively designed efficacy studies.

But again, the same message comes across. The data from all of these different studies strongly suggest the additional benefit of the recommended bivalent booster vaccines. You heard quite a few of these already this morning. the bottom two studies are, we didn't talk about. One, the Arbel study is of the study from Israel. The one on the bottom I just added in the last two days, is a study of children in North Carolina. Again, the take home message is the same. All of these studies point in the same direction that there is measurable effect, that there is measurable additional benefit from the recommended booster vaccines. And again, I find this pretty remarkable to see this kind of uniformity in the trend of the results.

The next slide summarizes where we are with vaccines containing an Omicron component. The preponderance of the data from vaccine manufacturers and independent researchers indicate an improved antibody response to SARS-CoV-2 Omicron variants following an mRNA booster vaccination with a recommended bivalent vaccine, which contains an Omicron BA.4/BA.5 component. I want to remind you that similar results were actually reported

for modified vaccine candidates containing an Omicron BA.1 component. We discussed this in the June 28th VRBPAC. I also put a sub-bullet here that, in that when we reported those data, = it appeared that the BA.1 neutralizing antibody titers correlated with the quantity of the Omicron component in the vaccine. This was true for both monovalent and bivalent vaccines. Now the reason I mentioned this is because to remind you that, in all of the studies we're talking about with these bivalent vaccines, we're essentially using half doses of the BA.4/BA.5 component. And I think that at least suggests that even further improvement may be achievable.

The second summary point is that observational effectiveness data strongly suggests that bivalent booster immunization provides protection against symptomatic infection. And as you heard in the other presentations today, also emergency department and urgent care visits and hospitalization. So together, the evidence that supports the use of a bivalent vaccine, which containing an Omicron component, together with recent preclinical data and clinical data with a bivalent vaccine use in primary series in young children, which we'll note again in a minute, together that suggests consideration of the same vaccine strain composition for primary and booster vaccinations.

Next, I want turn to topics that we're going to have for discussion. The next slide, approaches to simplified COVID-19 vaccination regimen, possibly leading to improved vaccine coverage, which may enhance the public health. And we think these should be considered.

The next slide. Simplification of the COVID-19 vaccination regimen may be feasible. Right now, we have multiple COVID-19 vaccine compositions. For example, different primary series and booster compositions. And these immunization schedules complicate the vaccine administration communication and update. We think that simplification of the vaccination regimen would contribute to easier vaccine deployment, better communication, and improved

vaccine coverage. Significant simplification of the COVID-19 vaccination regimen could be affected by adopting three things. One, the same COVID-19 vaccine composition for primary series and booster vaccination. Two, a simplified immunization schedule that applies to all Covid-19 vaccines. And three, the same vaccine strain composition for all spike-based COVID-19 vaccines. This is course we've talked about before. This is hopefully will be a data-driven vaccine composition recommendation made by the FDA after consultation with the VRBPAC.

Go to the next slide, and I'll talk about the alignment of the primary series. So recent data support an alignment of the COVID-19 primary series and booster vaccine composition. At the present time, as you know, the primary series vaccines remain monovalent, coding or containing an ancestral SARS-CoV-2 spike protein. This results in a complex vaccination program. Now, there were several reasons why, in June, we did not consider, and we collectively the FDA and the VRBPAC, did not consider the recommendation for a bivalent vaccine for the primary series. One reason was, of course, there was very little data to help us decide whether it was applicable for a primary series. There was nothing at the time that we could turn to. There was also some data at that time that made us wonder whether, that was in the literature, that suggested that Omicron might not be as immunogenic as earlier strains, and therefore may not lead to as good of a cross reactive antibody response as earlier strains. Now we know a lot more. And it turns out that's probably not that important, because that cross reactivity to earlier strains, well, those earlier strains simply don't exist. And it doesn't seem to hold true for later derivatives of Omicron.

And finally, there was probably a consensus to move conservatively at that time in June. And the WHO had not recommended changing the primary series. And I think the committee felt more comfortable taking a conservative approach and making the recommendation only for

booster strains. But we know a lot more now. As I've already said, right now, we've evaluated these booster vaccines containing these bivalent vaccines and the available immunogenicity and effectiveness data support the use of these COVID-19 vaccines bivalent vaccines for booster vaccination. I think the data is pretty clear. We also have now recent preclinical and clinical data that indicate the use of bivalent vaccines will improve the antibody responses against Omicron variants when used in either naive animals or as a primary series vaccine in young children, respectively. I've listed, the first two references listed are preclinical studies with Moderna and Pfizer BA.4/BA.5 bivalent vaccines in naive animals. These have been come out in print in the last few months, and then you heard earlier today Moderna's data for a study of a bivalent vaccine containing a BA.1 component when used as primary series of vaccine in young children. So I think the data is pretty reassuring and support this alignment of a primary series in booster vaccine composition. A move to such a single vaccine strain composition for primary and booster vaccination of the US would also align with a recent recommendation from the EMA, the European Medicine's Agency Emergency Task Force.

Okay, and go to the next slide. I want to mention the second discussion question we're going to have, and this has to do with a simplified immunization schedule, which could be considered for future vaccination campaigns. A little background first. An immunization schedule for future periodic COVID-19 vaccination campaigns would be simplified if a single dose of vaccine provided substantial additional protection for most individuals regardless of known vaccination status. In other words, no prior vaccination, primary series only, primary series plus one, two, or more booster vaccination. I think at some point in the States, most people would agree that at some stage of the pandemic, maybe even now, such an assumption will be reasonable. And a single vaccine dose should suffice for most individual due to the preexisting

immunity that has been acquired from prior infection, vaccination, or combination of vaccination and prior infection. A robust review of population level data should be capable of defining the age groups that would have acquired preexisting immunity. Similarly, a review of population level data should be able to define age groups that are effectively naive due to lack of virus exposure and vaccination. For such individuals, for example, young children without evidence of prior infection or vaccination, additional vaccine doses might still be needed to establish the protective immunity before any sort of periodic vaccination. A risk-based analysis should be able to identify other groups for whom an alternative immunization schedule might be needed, like the immunocompromised and guide the development of our appropriate strategy.

The next slide shows a schematic of a proposed simplification of the COVID-19 vaccination regimen. We recognize that additional data needed to pursue a simplified periodic vaccination strategy may be needed. it may include some, a better understanding of age-based rates of virus exposure and vaccination and identification of risk groups that would benefit from an alternate immunization strategy. But an example of a proposed simplification vaccination strategy is shown in this slide, and we can use this as a starting point for discussion, which we'll get to in a few minutes. You saw this earlier in the day, but the general scheme is what I outlined in the previous slide. For most of the population, the general population, which is adults, older children, adolescents, young children who've been immunized, it's likely that a single dose of vaccine would be sufficient. Because most of the, these people, this group, these groups have, are presumed to have had significant S-protein exposure such that a single dose of COVID-19 vaccine induces or restores vaccine effectiveness. In this, on the other hand, as I said, we should be able to identify risk-based adjustments for other groups such as high-risk older adults, persons

with compromised immunity, and young children who have not been previously immunized. And again, this will be the starting point for our discussion in a few minutes.

The next slide I want to turn to, I think the last topic that I'm covering, and that is the process of updating the SARS-CoV-2 strain composition, which we view and feel will be a continuous process. Go to the next slide. Strain composition of COVID-19 vaccines may need periodic updating. Since broad spectrum, variant-proof vaccines do not yet exist, current spike based vaccines may need periodic updating to maintain effectiveness as SARS-CoV-2 continues to evolve. A tentative framework for addressing future COVID-19 vaccine strain composition was proposed back in April. The committee had a vigorous discussion about this. Since that time, and since our June meeting, manufacturers have requested additional details and clarity about the process for updating the strain composition of COVID-19 vaccines. Specifically, they have asked about timing, process and methodology for making a strain composition recommendation, and the data package needed for manufacturers for authorization or licensure. I'm going to go through each of these in just a little bit more detail. You can start with the timing, which is the next slide.

Okay. Timing for the vaccine strain composition review and recommendation. There are practical considerations that suggest a limit to how often such a vaccine composition changes can be implemented. And these include manufacturing constraints. It also includes the availability, the timing, and the availability of sufficient high-quality data on which to base the recommendation. Based on our one in of one 2022 experience, a late spring, early summer annual target for review VRBPAC discussion and recommendation seems reasonable and practical. We did hear a few minutes ago that maybe that's not true for all vaccines. So again, that was why we asked each manufacturer to talk about this. But anyway, we threw this out as a placeholder as a possibility for some time in the late spring.

The goal of that meeting, of course, would be to review the current situation, to reassess where we are with current vaccines, how well they're covering, how well they're doing, and decide if improvement is needed and could offer benefit. The object, of course, before anyone says anything, is not to chase variants. I, none of us think that's realistic, but I think our experience so far with the bivalent vaccines that we have do indicate that we can continue to make improvements to the vaccine. And that would be the goal of these meetings. To get together, ask ourselves, can we make improvement and decide what is feasible? Of course, the emergence of a more pathogenic escape virus in the context of a public health emergency would prompt an ad hoc meeting of the VRBPAC. We have done that previously for influenza, for example, in the 2009 pandemic. If that were to happen again, I think we've shown that we can flexible and we be prepared to respond as needed if something like that happened.

The next slide. This slide, I cover a few details about the proposed process and methodology for making a strain composition recommendation. And again, we've talked about this a little bit at previous meetings. The evidence used to determine the need for updating a strain composition of COVID-19 vaccines would ideally include multiple types and sources of data, epidemiological and clinical surveillance to identify newly emerging, increasing and/or increasing COVID-19 outbreaks or epidemics, particularly any associated with increased transmissibility and/or clinical severity. Data would include virus surveillance, genomic analyses to identify these virus variants as well as their antigenic characterization to identify antigenically distinct variant viruses. We would also like to have integration of epidemiology, genomic analysis, and antigenic character rate characterization in order to conduct antigenic mapping and fitness forecasting. We would also like to have post vaccination human serology studies to evaluate the protective immunity offered by the current vaccines against antigenically distinct

circulating virus variants. And I want to come back to this in just a second. And finally, we would hope that when we do these reviews with the VRBPAC, we would have vaccine effectiveness studies to assess the effectiveness of current vaccines against co-circulating emerging variants and to help guide our guidance on the need for updated vaccines.

All of this, the data needed to make the recommendation for all vaccines. We need robust data for string composition, and I think we all think that it requires a coordinated effort of manufacturers, regulatory agencies, other public health agencies. The reason I stress this is because this is particularly important for the fifth bullet about post vaccination human serology studies. These are going to be critical that these studies be somehow that we have access to good vaccines sera and that the studies are done in a systematic, standardized way so that we can evaluate the results to make the best choice for going forward. The next slide.

Now I turn to the third thing I wanted to mention, and this is the proposed data package needed from manufacturers for authorization and licensure. I say at the start, this data package is different from the one I just talked about. The previous slide, I talked about the data needed to make a strain recommendation for all vaccines. Here we're talking about the data needed from each manufacturer. Each manufacturer would prepare a comprehensive data package for regulatory review of their updated COVID-19 vaccines that follows the recommendation that the FDA and the advisory committee has just made. That submitted data would include chemistry manufacturing control data for the updated vaccine to ensure product quality and consistency. That data might be different for different vaccines. We would expect that each manufacturer would have some preclinical data to support the effectiveness of updated vaccines.

The need for clinical data prior to authorization and approval would be based on several criteria. And so we, in a sense, this would be done on a case by case basis. But that criteria would

include the experience of each manufacturer, the genetic and antigenic relatedness of the updated strain component to previous vaccines, as well as some prior demonstration of efficacy with a specific vaccine platform. Regardless of whether we get clinical data, is we, whether we decide clinical data is needed before authorization, it is still needed after authorization. That clinical data post-authorization or approval would be crucial for an ongoing evaluation of the vaccine composition process. Next slide. I have one more.

This you saw at the very start of the day. This is a schematic of the sort of things I just talked about. Three steps. And again, you've already seen this, but basically step one, we review that data to determine the need. And I outlined the type of data we need. The VRBPAC makes a recommendation. Each manufacturer that wants to make an updated vaccine will do so. They'll submit their data package to the FDA containing CMC nonclinical, as well as get started on the clinical immunogenicity studies they're doing. We would then approve those vaccines for either EUA or approval. And then sometime later in the year, as data rolls out, data follows the rollout of those vaccines, we have real world evidence for their effectiveness. And that data would help us for the next campaign. This could be annually. As I said earlier, circumstances could dictate that it happens some other time, but this would be the general scheme for it. And I think that's the last slide before I have the discussion topics, which you've already seen. And I don't know if you want to go through these now, you saw them earlier in the day or not, but I'll stop here.

Oh, well, I can read them. We have one voting question and that's for does the committee recommend harmonizing the vaccine strain composition of the primary series in booster doses used in the US to a single composition? And the example we gave was, right now, that would mean the composition of all vaccines currently administered would be a bivalent vaccine. We have two discussion topics. Next one. Next slide.

One discussion topic will be about vaccine composition. Please discuss and provide input on the consideration of periodic updates to COVID-19 vaccine strain composition, including the currently authorized or approved vaccines to be available for use in the US in the upcoming 2022-23 season. And the second discussion question, which is a little more complex, is simplification of vaccine use. Please discuss and provide input on simplifying the immunization schedule to authorize or approve, a, one dose for most adults, adolescents, older children, young children who are previously immunized, and additional doses for higher risk older adults, persons with compromised immunity and young children who may not have been previously immunized. And that really is the last one. Thank you.

Q & A

Dr. Perlman: Thank you, Dr. Weir. So I want to say at this point we have time for just a, a couple of questions for Dr. Weir, but after a very short break, we're going to have the CDC, FDA, and sponsor presenters come back on. So, unless these questions have to be specifically for Dr. Weir, we might want to just hold them to that discussion period, because we really only have about five minutes total for talking to Dr. Weir about specific questions. So with that, Dr. Offit?

Dr. Offit: Right. Thank you, Dr. Weir, for that clear summary. There are a couple things that were said I'd like clarity on. One that surprised me was when you liken the Omicron strain to a shifted virus. I mean, clearly this is an immune evasive strain, but it's evasive really for protection against mild disease. If you've been vaccinated or naturally infected or both, you generally are protected against severe disease. And that was true ever since Omicron raised its

head in southern Africa and then spread out. I mean, a shifted virus. If we really ever do see a shifted virus, we're starting all over again. And that is not this virus. And we certainly need to be prepared if that ever happened. But that's not this virus. This is really much more analogous to a drifted virus. The second thing is that —

Dr. Weir: Well, I would only argue with you in the sense that up until Omicron, all of the drifting had been 1, 2, 3 amino acids, and then all of a sudden it was 35 different amino acids. It was quite a dramatic change.

Dr. Offit: Right. But you still, I think still you had, what you still had was a relative conf — you had these conformationally similar epitopes recognized by T and I think that's why. That's why I actually has drifted not shifted. I mean the good news is ever since you know, Wuhan won up until XBB.1.5, you still have conserved T-cell epitopes of 80 to 85%, which is why we're still protected against severe disease. Thank goodness. In any case. Second point, which I think is the more important point because it gets to the strain composition. You alluded to the fact that when you look at these bivalent vaccines, you do see an increase in neutralizing antibodies. Which, one could argue whether those are clinically significant increases and whether we've had studies that clearly show that this is clinically better than what we had. But the thing I'm wondering about, because you had this paper that was mentioned by Dr. Das, it was just published yesterday out of the United Kingdom. And now this paper by Whitaker that was just published in new England Journal of Medicine, that we're all — Both those studies are looking at sort of these monovalent vaccines against, you know, these Omicron variants where you're giving 30 or 60 micrograms for Pfizer or, you know, 50 micrograms for Moderna. Do you think that's where we're heading? I mean, do you see us heading? Is that what you mean when you talk about improving those

vaccines, where we wouldn't be then using the ancestral strain anymore? And is there still a reason to use the ancestral strain? And I'll stop. Thank you.

Dr. Weir: I can give you an opinion, but that's all. First of all, I think this is exactly the sort of thing that we would discuss at the next VRBPAC where we talk about a strain composition. I think it would be a debate worth having, when fact, it'll probably be needed. We will need to have it, of whether we should continue something like a bivalent vaccine containing a strain that hasn't existed in three years versus trying to tailor it more. I don't know the answer. My gut feeling, which, I mean, my gut doesn't produce the data, but my gut feeling is that a monovalent would've been a little better now than the bivalent. But I think there were reasons why we chose the bivalent, which were pretty good at, at the time. But to answer the real question, where are we headed? I don't know. I think we evaluate the data, what we have at the time. We feel like we need to make a new recommendation and we make the best choice that we can. If that's a bivalent, maybe that's what we do. If it's a monovalent, that's what we do. But I think we just follow the data we have.

Dr. Offit: Thank you. Thank you, Jerry.

Dr. Perlman: Okay. Dr. Levy?

Dr. Levy: Yes. Wanted to thank Dr. Weir for his presentation, and the framework is very logical, and I'd like to thank FDA for pulling all this together. One of his slides talked about, well, maybe a single dose would suffice given in the fall. And I think we need, and I know he knows this, but we all need to think suffice for what, what are the goals of this program? Obviously we're trying to prevent death, and we're pretty good at that, ICU admission, but are we also targeting mild to moderate disease infection? And of course, this gets back to immuno-

bridging the antibodies. What are the correlates of protection, which may vary of course, for each of these endpoints that we're trying to achieve? And then we're talking about infants where the correlate of protection may be distinct. So does FDA plan moving forward to analyze the correlates of protection for the different desirable endpoints in a population specific way?

Dr. Weir: Okay. First of all, I think you're right. This is an extremely important topic. You heard a little bit from the NIH presentation from Dr. Beigel. This is something that not just the FDA, but the government, is interested in. We would like to have that information. I think everyone would love to have it. I will just counter by saying it gets, it's difficult to obtain and it's probably getting more difficult to obtain those correlative protection data for Covid vaccines at this point. I definitely think everyone will keep trying and hopefully more information, more data will become available over time. But yes, we're all interested in it.

Dr. Levy: Thank you. Certainly with naive hosts, it may be easier. Thank you.

Dr. Weir: Yes.

Dr. Perlman: So, Dr. Chatterjee, do you have something you want to ask Dr. Weir? Should we put it off to the discussion in 10 minutes?

Dr. Chatterjee:I'd actually like to ask Dr. Weir if I may, Dr. Perlman.

Dr. Perlman: Okay.

Dr. Chatterjee:I'll make it quick. I actually have two questions, but I'll ask the first one and see if you have time for the second one. So the first one's actually pretty simple, which is, Dr. Weir, you talked about, you know, the different manufacturers and the timelines and all of that and them updating the vaccines. What if a manufacturer decided not to update its vaccine? Would the

FDA then withdraw the EUA or licensure of that particular product that they were using? Or is that not a topic that has been discussed so far?

Dr. Weir: It's probably not a topic that I can give you a definitive answer on today. It's not one that we haven't thought about, but I would have to, we would have to have a serious internal discussion about how to approach that.

Dr. Chatterjee:Okay. And Dr. Perlman, do we have a moment for my second question?

Dr. Perlman: If it's even faster than your first one.

Dr. Chatterjee:Oh, I'm very fast. This is actually a question slash comment, and that is I would encourage the FDA, if they have not already thought about it, to plan for a full licensure type approach rather than EUAs for these vaccines going forward.

Dr. Weir: We've definitely thought about it.

Dr. Chatterjee:Thank you.

Dr. Perlman: Okay, so what we have now is we have a short break, initially was for 10 minutes. I wonder if we can do it for less, while we get the people from the CDC, FDA, and the sponsors back in the room. Suzanne, can we do it for less than 10 minutes, or do we need 10 minutes?

Dr. Paydar: Let's do less than 10 minutes.

Dr. Perlman: Okay. So let's come back in six minutes.

Additional Q&A for CDC, FDA and Sponsor Presenters

Dr. Perlman: Okay, welcome back. So at this part of the session, we are going to have folks from the CDC, FDA, and sponsors answer questions that we couldn't get to before. So to start this off, Dr. Rubin.

Dr. Rubin: Thanks, Dr. Perlman. Question for the three presenters from earlier, on safety. I really appreciate the fact that they presented data that's somewhat contradictory on the safety related to stroke. And I appreciate it because we should be able to handle those sorts of data. They're real. But I'd love to get their take on the public message. What should someone who is listening in from the public take away on the safety of vaccines relative to ischemic strokes?

Dr. Shimabukuro: Hi, this is Tom Shimabukuro. Can you hear me?

Dr. Perlman: Yeah, we can.

Dr. Shimabukuro: Thanks. I mean, I'll just reiterate that CDC continues to recommend that everyone eligible for a COVID-19 mRNA bivalent booster or a flu vaccine get vaccinated. I mean, we detected a statistical signal, and we are in the process of assessing that signal. And I don't think the evidence are not sufficient to conclude that there is a safety problem with respect to stroke. And the CDC recommendations are that everyone who's eligible get a bivalent booster. And we'll continue to do more work on this. And also, as Dr. Forshee mentioned, additional more formal epidemiologic investigations. And we'll continue to, we will make information available as it becomes known to us.

Dr. Forshee: And this is Rich Forshee. Just add a little bit to what Tom had to say. I think the public should know that we have multiple systems in place to try to look for any potential safety signals with the vaccines. And we really treat it as a system where we have these early warning systems to try to know if there's some hint that we need to further evaluate, and then we move on

to do more rigorous testing afterwards. So with the multiple systems in place, it is not at all surprising that we sometimes get signals in one system, but not in another. And we then need to do the hard work of evaluating it more rigorously. Thank you.

Dr. Rubin: Thank you.

Dr. Shimabukuro: If I could just follow up to Dr. Forshee's comment, and just reinforce what Dr. Forshee mentioned. I mean, our systems are designed to be sensitive, to broadly capture potential safety concerns and to be able to rapidly assess those concerns. And I think what you heard this morning with the CDC and VSD presentation and the FDA presentation, and the thoroughness in which these findings are being assessed demonstrates that the safety system works. And you basically saw that process in action working. And I think the public and the medical community should be confident that the government has the systems in place to rapidly detect potential safety problems and assess them. And we place a priority on communicating in a timely and transparent manner.

Dr. Perlman: Okay. Thank you. Dr. Gans?

Dr. Gans: Thank you so much. The question I had for the safety — I have different questions for different people. I'm not sure how to handle that, but my question for the safety people is, I do think that you very well articulated the current VSD and the rapid cycle, and all that is very encouraging and is really robust. I guess the question that I would have is how overall are we also handling some other potential ways in which these vaccines are impacting our population? So obviously we heard some reports and there's some data out there. So how are we tracking, for instance, potential autoimmune and other of those entities that maybe aren't amenable to the rapid cycle? That's my question for the safety people. Do I just get back in line

for the vaccine groups, or how do you want to handle that. Or should I throw it out there and they can answer it?

Dr. Perlman: Why don't you throw it out there now?

Dr. Gans: Okay. So my question for the Novavax group is, is there going to be peds data that is going to be looked at, and then will we be, will that be available to us? Because I think what I heard mostly was non-pediatric data. And then from all the groups, I would love to know about a bank of, as we saw in one of them, I think it was the Moderna, a bank of preclinical data that maybe doesn't include the ancestral strains. So we can start to answer that question in these other strains. And if they're going to have more broadly immune studies, as we've heard asked for. And we know they're difficult to do, but we really do need them, which would include BT and mucosal immunity.

Dr. Shimabukuro: So, do you want, would you like me to address the first question?

Dr. Perlman: That would be appropriate.

Dr. Shimabukuro: So, you're correct that in, in our vaccine safety datalink rapid cycle analysis, our outcomes are pre-specified. We have in our Vaccine Adverse Event Reporting System, or VAERS, we do not pre-specify outcomes. That is a spontaneous reporting system, and anyone can report. A patient, a parent, a healthcare provider, and we accept all those reports without judging the clinical seriousness or how plausible the adverse event may be with respect to causation. So we do have other systems to monitor outcomes beyond the rapid cycle analysis outcomes that were presented earlier today. At CDC, we also have a group called the Clinical Immunization Safety Assessment Project, which does detailed clinical case consultations at the request of healthcare providers. So we take vaccine safety very seriously.

With respect to reports of people experiencing debilitating illnesses. I mean, we are aware of these reports of people experiencing long-lasting health problems following Covid vaccination. In some cases, the clinical presentation of people suffering these health problems is variable, and no specific medical cause for the symptoms have been found. We understand that illness is disruptive and stressful, especially under those circumstances, and we acknowledge these health problems have substantially impacted the quality of life for people and have also affected those around them. And we hope for improvement in recovery. And we will continue to monitor the safety of these vaccines and work with partners to try to better understand these types of adverse events.

Dr. Perlman: Okay. Thank you. Dr. Dubovsky, do you want to take the second part of that question?

Dr. Dubovsky:Sure. Yeah. Right. So in the US we're authorized for age group of 12 and above. We're currently in the midst of our pediatric development. We're vaccinating downward children as young as two years of age, currently in the US, with the plan to escalate down to six months of age after we hit the safety cohorts. I should say that there's a pre-publication available on the archives. Our partners at SerInstitute of India, where they're publishing data for their pediatric study. And in India, the vaccine's authorized above s seven years of age. Okay.

Dr. Perlman: Thank you. Dr. Pergam?

Dr. Das: You know, if I could, I can take the library question. You know, we showed our library of variant vaccines, which we add to every month based on our ongoing viral surveillance and risk assessment. And this allows us to be prepared for future strain selections. We, of course, also remain vigilant to be prepared to respond to an off-cycle strain selection for an immune

evasive event. Last year we produced the BA.4/5 bivalent vaccine in 90 days, and that timeline is aligned with FDA's proposal. And we welcome continued conversations with FDA, this committee, and the CDC about future strain selection.

Dr. Perlman: Okay, thank you. Dr. Pergam.

Dr. Pergam: Yeah, thanks Dr. Perlman. This is sort of a, a follow up on, on Dr.

Gans's question. A little bit about the pediatric population. It feels like we're getting to a space where there is either people that have received a number, at least a series of vaccines who have been infected by at least one strain of Covid at some point. But the pediatric population still remains different, especially the very young. And I'm curious from the FDA's perspective, if we are to switch to a new strain or a new vaccine, a bivalent, as the primary vaccine series, is there going to be an effort to do initial studies looking at these vaccine strains or these vaccines and their efficacy data in terms of primary vaccine series? That's what we saw a little bit, I think, with some of the Moderna data. And then as a second question you know, there's been a lot of discussion about the general population, but I'm curious how the FDA is going to be approaching immunosuppressed populations. Particularly since the series and the number of vaccines given has been varied over the past few years. And so I'm curious how they're going to address that particular population as we move forward with these new vaccine recommendations. Thank you.

Dr. Perlman: Dr. Forshee, I think that's yours.

Dr. Forshee: So I would actually hope that some of my colleagues from OVRR might be able to contribute to this as well. So is Dr. Weir available to talk a little bit about this?

Dr. Marks: This is Peter Marks. Hey. So, thanks. Thanks very much. So I think we recognize that for the immunocompromised — and this is, I think, one of the things we need to discuss today — we've had multiple vaccine. And for the mRNA regimens right now, it's been an extra vaccine as part of the primary series. And whether that translates into two vaccines per year or what it would for an initial vaccination, I think that's something that we'd like to have a discussion of and use the best available data that we have. Part of this is too, right, the immunocompromised are a real spectrum, because the modest immunocompromised of a diabetic compared to the tremendous immunocompromised of somebody who's received CD20 depleting therapies. There's real spectrhere that we're dealing with. Over.

Dr. Perlman: Thank you. Dr. Berger?

Dr. Berger: Hi. Thanks, Dr. Perlman. This is actually a holdover from this morning when Dr. Scobie gave her presentation on epidemiology, what's going on currently. I really appreciated the information on hospitalization rates and other impacts. And I was wondering if there were any granularity that the CDC has been collecting, for instance, on length of stay or at least severity after hospitalization from this. I think one of the purposes here that I think we're hoping the vaccines can do is not, you know, keep the healthcare system from being overwhelmed and ensure that that capacity remains where it's needed. So it's just a real question about what kind of granularity might be available on hospitalization rates at the moment.

Dr. Jones: I'm afraid Dr. Scobie wasn't able to make this. Dr. Jones. So for our hospitalization data, we do have platforms such as Covid-Net that do include length of stay and therapies given, ICU admission, oxygen, et cetera. And we are able to have and will continue to publish on that data. For post-hospitalization, those would require different platforms. We have a number of platforms more looking specifically at post-Covid conditions, which is perhaps a little

bit different than what you're talking about. So I think we, there may be — which is something we haven't talked about a lot today, but that would be the main, one of the main focuses we're looking at. Hopefully that answers your question. Happy to clarify.

Dr. Perlman: Thank you. Dr. Gellin.

Dr. Gellin: Can you hear me? My camera's not working. Can you hear me?

Dr. Perlman: Yes.

Dr. Gellin: Okay. Thanks. Two questions. One for CDC, one for FDA. I think that the CDC is about timing. When in the calendar do we want to have, on a population basis, optimal protection? Getting, this is the seasonality question. And because, and then with that, that then begs the question of when vaccines should be available, when vaccination should commence, and incorporating waning. And then for the FDA about composition, the CDC data about the diversity of variants around the country is really quite revealing, and we didn't see anything about the rest of the world. And I guess that begs the question of, we've seen in the background documents about coordination with WHO. This has all been a US, maybe Northern Hemisphere based conversations. How is this going to happen with the rest of the world? Thanks.

Dr. Jones: Apologies. I'm not sure who you want to answer the question, but just as — CDC, about seasonality. We have generally seen peaks during the winter months, but there's certainly been inter-seasonal peaks as well. And I think additional data will be needed to be, additional seasons will be needed. But agree with FDA's approach of fall campaigns to be in anticipation of maximum protection against both severe disease and infection during expected peak months during those winter months.

Dr. Gellin: Can I ask, did you, have you wound back the clock and said, had you had this in place with a June selection in the past two years with a September availability, how that would've played out? And is that the right, you know, what's that look like?

Dr. Jones: So is the question of how many additional, perhaps hospital —

Dr. Gellin: So the question is if this policy was in place three years ago, June selection, September vaccine availability, if you looked at what was available to, took a snapshot in June and that vaccine showed up in September, how would that have worked for the fall and winter that followed?

Dr. Jones: It could, it would be likely take a fairly complex model to really plan that out as far as, say, largely Alpha and some Delta into a winter with Delta and then Omicron, and how vaccines focused on those antigens may or may not have had improved protection over the initial vaccine. And the same for the following year. I think it's a fairly interesting and complicated question. That we'd assume there'd be some improvement, but it's hard to anticipate exactly how much that would be.

Dr. Marks: This is Peter Marks. From the FDA perspective, I think that we're starting to see some seasonality, as was just now noted by Dr. Jones. And I think we also see the potential advantages to the winter seasonality with a fall campaign, because when do we have to worry about the worst overwhelming of the hospitals? It will be when we have influenza, RSV, and potentially Covid at the same time. And the advantage of this also is that, if we can see influenza vaccine and the COVID-19 vaccines occurring at the same visit, again, it facilitates a vaccination program that may lead to more people getting vaccinated and being protected and reducing the amount of disease we see. So I think that overall this seems like a reasonable way to go. I'll let

Jerry Weir comment as well, but we're very much of the mind that we would like to work with our global partners, including WHO and other regulatory agencies, to make sure we're well coordinated here. It's just a matter that not every regulatory agency and WHO are not, perhaps, at the same place right at this very moment. But ultimately, we totally understand the need to have global surveillance, global coverage of these variants and ultimately good coordination with all of our partners.

Dr. Weir: Yeah, this, this is Jerry. I, I think you pretty much covered it, Peter. One thing I will add is that the WHO does have a group that monitors variants and at least occasionally makes recommendations. They don't have a set schedule for when they do this. About six months ago, they did invite us to join that, and I think that, and we enthusiastically accepted, although it's still in the works to for it to happen. But we will clearly participate in that if we can work it out. You're right, though, that unlike flu, the global distribution of variants is more variable. And that's one reason I mentioned in my slides, I like that website that's called Covariants, because you can click on every country, and you can actually see in real time how this differs. So going forward, it is still challenging. Variants don't sweep across the world quite uniform like they do, like they seem to with influenza. But yes, we'll continue to work with our partners throughout the world as best we can. But our primary responsibility is what's best for the US market, and that's where our focus will be. Over.

Dr. Perlman: Okay, thank you. I just want to make one comment. We have a lot of questions. I'm not going to cut them off, but if questions are comments, and they haven't been, but if there're going to be comments, can we just save them for the next section? Because we're going to run out of time. So Dr. Nelson.

Dr. Nelson: Thank you. I've got two questions. One for is an extension of the last one regarding seasonality. So I appreciate the question from Dr. Gellin and Dr. Marks's remarks. I too had designed, or hoped that we could design, the release of the vaccine along with the influenza vaccine, but I noted from the data presented this morning and previously that there is some seasonality. Yes, the predictable winter peak, but there also seems to be a late summer mini surge as well, if you will. My question to the CDC is, are these two peaks distinct or are they somehow connected? And that perhaps targeting even the earlier peak may have some benefit in lowering the magnitude or severity of that second winter peak, which might make timing of release along with the influenza vaccine a little more challenging. And I'll ask my second question after the response.

Dr. Jones: I think it's a little bit too early to really predict with certainty if there will continue to be a big peak and a small peak. I mean, compared to other pathogens, it's been a relatively recent, you know, just a couple, two, three years of data that we have to observe. As far as, specifically, is transmission from the smaller peak related to the greater peak? Well, recency of infection does affect your ability to be protected from infection and therefore transmission. We do have transmission modeling teams that are working on various questions, and that's an interesting one for us to look at.

Dr. Nelson: Great. Thank you very much. Second question is regarding safety. So again, congratulations to the team for your aggressive approach in using multiple systems to identify signals and really providing some reassuring safety data for the vaccines that have been released to the public. My question is regarding some of those rare adverse events, one of my areas of interest. Can we also reassure the public and this committee, if you will, that there are mechanisms in place that look at not only signals across the entire population, but identifying

more rare adverse events and whether there are subpopulations with enhanced risk that we might be able to identify and perhaps better shape recommendations for vaccinations? Over.

Dr. Shimabukuro: I think I can make a general comment that, you know, in our VAERS system we do monitor again for all adverse events, and we do attempt to, at least for serious adverse events, we attempt to follow up and get additional medical records and information, which may shed light on the condition of the individuals experiencing the adverse event. If there were particular concerns in subgroups, I think, ultimately, we would probably have to do epi studies to look in those specific subgroups. But in our monitoring for serious rare adverse events, we do attempt to get as much clinical information as possible to assess comorbidities and existing conditions.

Dr. Forshee: And I would just add that we do have a good bit of experience working with some very rare adverse events in our vaccine safety monitoring. In our flu safety surveillance, for example, we regularly monitor Guillain-Barré syndrome, which is a very rare outcome. And so we've been able to detect risks below one in a hundred thousand in terms of attributable risk. So because of the size of some of the systems that we use, we are able to accurately estimate what the risks are for low risks or for subpopulations. And we have examples with previous vaccines where we've demonstrated that capability. And a lot of this has been done in conjunction with the CDC.

Dr. Shimabukuro: Let me just quickly follow up. I had mentioned previously our Clinical Immunization Safety Assessment Network. So that's a collaboration between CDC and academic medical centers and medical research centers and with access to specialists and subspecialists, where if we do get, at the individual level, we do get a report of an adverse event in a patient

with a comorbidity or an existing condition, we do have the ability to do in-depth clinical reviews of those cases and get feedback from our specialists.

Dr. Nelson: Yeah, I'm very familiar with the great work of the CISA and its origins in my former position of the Department of Defense. And I think it highlights the communication problem that we've had and that we're great at identifying the absence of big signals and not really fortifying that with, yes, we continue to look for those rare signals, and yes, the individual events occur, but not to the point where at which there needs to be a change in recommendation. So thank you all for your great work.

Dr. Perlman: Okay, so at this point, can people try to have just a single question, because we're really running out of time. Dr. Bernstein.

Dr. Bernstein: Sure, I had two questions, but I'll stick to one as you said and maybe ask the other later. There's been a lot of emphasis on neutralizing antibodies, but personally I think more T-cell data would be incredibly helpful. And that being said, is it known what the ideal amount of antigenic content and from which strains are needed for durable T-cell memory by age? Because we're talking about, it's been mentioned about even having a bivalent vaccine for the primary series, especially in young children. And I certainly would not want to, I would still want to maintain the T-cell memory with whatever vaccine plan we put in place.

Dr. Weir: This is Jerry. You were breaking up a little bit, but I think I got all of it. The short answer is no, it's not known. And one other thing everyone needs to keep in mind is a T-cell response is a broad term. I don't even think we know whether the T-cell response is a CD4 C-cell response, a CD8 response. There's even, I'm just saying there's a lot that's unknown. But the, how

much of that would contribute to protection and how it contributes to protection? I think there's just so many unknowns. Unfortunately.

Dr. Bernstein: I do think it's making a difference though. I think it's what is presenting people from —

Dr. Weir: Nobody argues that. Nobody argues that. I think we all agree that it's important. The real question is what is its relative role and how do you measure it if you really want to know how it contributes, especially to something like severe disease versus symptomatic, that sort of thing. It's just really hard to know at this point in time.

Dr. Perlman: Dr. Cohen?

Dr. Bernstein: I'll stop. I have another one for later.

Dr. Perlman: Yeah, we'll have discussion time. Dr. Cohen.

Dr. Cohen: I have one question for the companies specifically. I was wondering if you guys could talk a little bit more about immunization in very young children and if you guys are planning or thinking about doing anything like different schedules and different lengths between doses to align more in the long term with our routine immunization schedule, or if there would be an advantage of having some better spacing between the doses to allow for better T-cell responses.

Dr. Das: Yes. Maybe I'll take it first. So we do have a study called Baby Cove. It is going to be, it started enrolling and we're dose ranging right now. It's in infants three to five months of age and we are using that eight-week interval to try to align with a kind of a routine pediatric

vaccinations schedule. And so we're going to select a dose and then we'll get into the placebo-controlled part of the study.

Dr. Swanson: So we also are also evaluating in children six months to less than five years of age. Both the current dose regimen for the three-microgram bivalent vaccine, but also extended intervals. You know, we started at the early days of the pandemic with that original schedule. So we're further studying the longer intervals to see if there's any impact on the immunity as well.

Dr. Perlman: Okay. Thank you. Dr. Reingold.

Dr. Reingold: Yeah. Hi. Can you hear me? So quick question in terms of what the package is that companies will be required to submit. You know, in the real world telling people like me the need to come in on separate dates for their flu shot and their Covid shot is certainly not going to improve coverage. And so are you going to require data about, I don't care if you use the word co-administration, concurrent administration, concomitant administration, but administration of the two vaccines on the same day. Thanks.

Dr. Weir: This is Jerry again. That is probably not something that I typically we would put in a package for an authorization or an approval of a strain change supplement. We certainly don't do it for influenza. On the other hand, those type of studies do get done at some point. I guess I would have to say we'll discuss it further about what type of studies like that would be needed from manufacturers if this becomes a major issue. I don't know if Dr. Marks or somebody else wants to add into to this.

Dr. Marks: So, this is Peter Marks. I would just add that we will be doing formal epidemiologic studies on co-administration of influenza vaccine with the COVID-19 vaccines in large databases. I think we'll have real world evidence. We may also have some companies that

are studying these together, and I think, point, very, very well taken that, I think as we move into the next fall, ideally, again, given that we were a little bit lackluster in our ability to get even the adult population vaccinated with boosters this fall, and even the older adult population, that being able to have the data so that we can do concomitant flu and Covid vaccination may be very helpful. So we'll take that back. Thank you.

Dr. Perlman: Okay. Thank you. Dr. Meissner?

Dr. Meissner: Thank you, Dr. Perlman. I've selected the most important question, because several of them have built up here. And I'd like to respond to Dr. Beigel's presentation, which was I thought very helpful, as well as his presentation at the NIH symposium a week or two ago. So, and I'm not sure if he's still on, but I will present the question. Do we really want to stop asymptomatic infections by SARS-CoV-2? First of all, I don't think that's a reasonable objective, at least with the current generation of messenger RNA vaccines. And you can certainly make the argument that an asymptomatic infection is desirable because it will stimulate both cellular and humoral immunity. It will kind of act like its own boost. So to me, we certainly want to stop the virus from circulating, but that's probably not going to be possible because the vaccine, as clever as it is, is always going to mutate and evolve, and, at least indefinitely, find ways of avoiding the immunity that humans build up. So do you really think that should be an objective of the vaccines? Over.

Dr. Perlman: Yeah, so I think that's a great question for the discussion, but John, if you want to say something briefly to answer that.

Dr. Beigel: Well, I was just going to say it's a discussion more than we can accomplish today. Certainly, decreasing the overall community load, if you decrease asymptomatic infection, you

decrease transmission, you can decrease that community load. I think that is the intent. There are some at least theoretical benefits, as you've articulated, and I think how you balance those just requires a larger discussion.

Dr. Meissner: Okay, thank you.

Dr. Perlman: Thank you. Dr. Lee.

Dr. Lee: Yes. I wanted to follow up a little bit on this question of giving the flu vaccine and the Covid vaccine at the same time. While I recognize that will probably increase adherence or uptake, one of the things that struck me, maybe something CDC can address this, is when I looked at the stroke data, I was sort of left with the question. I know most of the people, I think, got the Covid vaccine probably in close proximity temporally to the flu vaccine. But is there any reason to believe that spreading those out temporally might reduce the stroke risk? Thank you.

Dr. Shimabukuro: So, the findings that were presented this morning on concomitant bivalent and flu vaccine were actually a post hoc supplemental analysis that was part of the original signal detection. There may be other reasons besides vaccination, while we're, for observing those findings, like unmeasured confounding or bias or other potential health systems issues. So I don't think that the evidence are sufficient to conclude that there's an association there. And given that, I think talking about spacing out the vaccines may be a bit premature at this time. And I'll just r reinforce the CDC’s recommendations for Covid vaccination and for flu vaccination ha have not changed.

Dr. Lee: Thank you.

Dr. Forshee: And I would just quickly agree with Dr. Shimabukuro. We are going to be doing a more formal epidemiological study in Medicare to explore that question to just get a better understanding of whether there is any relation, any interaction there.

Dr. Perlman: Okay. Thank you. Dr. Kim.

Dr. Kim: Well, thank you, Dr. Perlman. Most of the discussions we've had today have, well, have revolved around the messenger RNA vaccine. But we did have the Novavax also present. And I have a question for Novavax and also a question for FDA. What's FDA's position and also disposition on the Novavax's protein subunit vaccine? And for Novavax, what is your current position on how your vaccine can be used in the context of today's discussion?

Dr. Dubovsky:Right. So maybe I'll jump in first. I mean, we are approved in the US for primary series as well as for boosting. Right now, there's no more individuals who need primary series. At least some, most, are talking about young children. So we think we're going to be important tool for boosting in this upcoming season. And that's how we think we should be used. And we think that there's, they've actually showed you today, actually supports use of our vaccine as a booster just because of the breadth of the immune response we induce. And we will be getting future variants from whatever strain is selected. We can't chase the strains. So in our opinion, it's better to use a vaccine that can induce these broad responses against the variant that will eventually emerge.

Dr. Perlman: Okay. Thank you. Does anyone want to address it from the FDA side?

Dr. Weir: This is Jerry. I thought Dr. Kim just asked what our position was on Novavax. Did I miss part of the question?

Dr. Kim: What are your thoughts, considerations, for the Novavax protein subunit vaccine in the context of what we're talking about in terms of primary series and booster?

Dr. Weir: Well, as you just heard, we've authorized Novavax for emergency use. So I guess that's our position. You heard today they were, they say they are able to, if a recommendation comes from this committee to update and change the vaccine, they said they are able and willing to do that. So I guess that's our position, that they would do that if the committee makes a new recommendation. So not sure what else to tell you except that we've authorized them, and that's where we are today.

Dr. Perlman: Okay. Thank you. Dr. Sawyer.

Dr. Sawyer: Yeah, I have a question for the manufacturers. It relates to the timing of strain selection and the distribution of a new product. And the specific question is, if each of the manufacturers could let us know if they're headed towards single dose vial distribution or single dose distribution. This is going to be particularly important as we move from government funded vaccine to privately purchased vaccine. In my community, most pediatricians only offer the vaccine on a few specific days of the week or times of the day so that they don't waste product by opening a ten-dose vial and not having enough patients to use that. And that's despite advice that that's okay to do, but it certainly will not happen if the pediatricians have to purchase vaccine and then use up a vial on the same day that it's opened. So we heard, you know, at least one of the manufacturers has gotten to two dose vials. I think I'm wondering what the future plans are and whether the hundred day timeline projected for mRNA from strain selection to product delivery would hold up if we needed single dose vials.

Dr. Perlman: So can I have the manufacturers very briefly answer that question.

Dr. Das: Sure, I can take it first. From Moderna. We certainly hear you and we are moving towards single dose vials and prefilled syringes just to facilitate just that. And we do think we can achieve that in the timeline outlined.

Dr. Perlman: Pfizer?

Dr. Swanson: Maybe I'll take it next. So, Dr. Swanson here. So similarly, we'll be transitioning from the multi-dose vial to the single dose vial going forward and can support that with the future vaccine updates.

Dr. Perlman: Thank you. Dr. Dubovsky, do you —?

Dr. Dubovsky:Yeah, it's, it's a similar situation. We're heading to a single-dose vial, and we're aiming to get to a pre-filled syringe shortly after that.

Dr. Sawyer: Great. Thanks very much.

Dr. Perlman: Thank you. Dr. McInnes.

Dr. McInnes: Hello. Thank you. Can you hear me?

Dr. Perlman: Yes.

Dr. McInnes: So I have this comment that I'm going to restrict to this particular phase of things. So I guess this is directed for Jerry Weir. So Jerry, I think we kind of move into this discussion that — can you see me — that COVID is kind of like flu, but actually Covid isn't like flu in many ways, except its waves. And we tend to try to treat it like flu and we think we can have a periodicity of the response, but actually bringing to operationalize how you might do that is actually the challenge. So, I see the suggestion that maybe by June is the good time to do, and it may be, it may be a perfectly fine time, but it seems to leave a very short time for manufacturers

who manufacture both vaccines, in order to get both of them on the dock. So I'm trying to, I'm sort of very, very sympathetic, by the way. I don't have to operationalize this, but COVID is not flu as an infection or a disease. So I'm wondering how you see being able to build in an operationalized periodicity versus the need to have a decision and move and how much flexibility the manufacturers have. So, I'm sorry, that's a difficult question.

Dr. Weir: Yeah, it's… Well, to start off, one of the reasons we asked the manufacturers to come to this meeting was to tell us how much time they need. So actually, I heard something today that I hadn't heard before today, and that was exactly how much time a protein-based manufacturer would need. We may have to go back and rethink this as far as the timing. As I said earlier, I put this out there as a placeholder. We would say we had an n of one this past year. We did it in June. It seemed to work okay. But, you know, I think, Dr. McGinnis, we're all just going to have to maintain flexibility.

Dr. McInnes: Yep. You're right.

Dr. Weir: There's not a good pattern yet.

Dr. McInnes: Yet. Right.

Dr. Weir: And, and I think we'll just do that. We'll look at this and we'll try to be flexible. We'll try to work with manufacturers to keep and get as many manufacturers on the market as we can. Because you and I have been through flu for I don't know how many years. I mean, having options is important and you never know which one you're going need. So we'll continue to do this. I think, you know, we'll be flexible, and we'll work with them as best we can.

Dr. McInnes: Thank you, Jerry. It's not flu though. We agree, right?

Dr. Weir: So I'm the first one to say you can take some lessons from it, but no, it's going be different. They are different viruses.

Dr. McInnes: Yep. Thank you.

Dr. Perlman: Thank you. Dr. Chatterjee.

Dr. Chatterjee:Yes. Thank you, Dr. Perlman. My question is for the vaccine manufacturers. So during the open public hearing, we heard about a combination influenza COVID-19 vaccine product that's been evaluated by a company. And I was just curious to hear from you all whether you are developing this type of product as well and where you are in the development phase for those.

Dr. Swanson: Maybe I'll start. This is Dr. Swanson from Pfizer. So we have initiated studies to evaluate the combination of flu-Covid vaccines and are in early studies for that. And as with all of our prior clinical studies, you know, robust safety assessments are a part of that trial as well.

Dr. Chatterjee:Thank you.

Dr. Das: And this is this is Rita Das from Moderna, and we have initiated a phase one trial for combination Covid and flu vaccines. Thank you.

Dr. Chatterjee:Thank you.

Dr. Dubovsky:Earlier this year we announced data from our initial studies for our combination product as well. And we just started a phase two study for combination influenza plus Covid. And we're anticipating that that data is going to be available kind of midyear to make a good decision on how to go forward.

Dr. Chatterjee:Thank you very much.

Dr. Perlman: Okay. So now we're going to stop this part of the meeting and go into discussion. So I'm not sure, do the sponsors and CDC and FDA stay on the line for this or how do we work this?

Dr. Marks: We do stay on the line.

Dr. Perlman: Okay, right.

Dr. Marks: And this will allow the committee members, if need be, to ask additional questions, although that's not the primary purpose. So I think we can get the questions up here. I'll turn it over to Dr. Kaslow.

Committee Discussion and Voting

Dr. Kaslow: Great. Thank you. Yeah. So let's go ahead and put the first voting question up, or the voting question up. So the voting question is does the committee recommend harmonizing the vaccine strain composition of primary series and booster doses in the United States to a single composition? For example, the composition for all vaccines administered currently would be a bivalent vaccine, original plus Omicron BA.4 BA.5.

Dr. Perlman: Okay. So we will discuss this voting question for the next hour or so, and hopefully answer all the questions.

Dr. Marks: I guess, Dr. Perlman, I think maybe it, maybe it's probably easiest to take these questions in succession and start with the voting question and then go to the discussion questions. Does that make sense?

Dr. Perlman: Yeah, that's what I was planning to do. And then we'll read the discussion questions in about an hour and spend, hopefully spend the last hour on that. We will probably go over our 5:30 deadline and go up to possibly six o'clock if we need the time. If we don't, that's fine too. So, Dr. Meissner?

Dr. Meissner: Yes, thank you. I had my, I had a question on the last session, because the risk of stroke seemed to be associated with adjuvant or high dose influenza, and I wanted to ask how they, the manufacturers, are going to address that that issue. But since we're in the next session, I think this proposal by Dr. Weir is reasonable. I think that certainly the vaccine strain should be harmonized among the different manufacturers. And, but the issue of how frequently they should be administered is hard to say with precision at this particular point. I think we need to see what happens with disease burdens. That is, we may or may not need annual vaccination. It's just awfully early, it seems to me, in this process to answer that question. And the last point I want to make is people spoke a lot about correlates of immunity in deciding on how well or how effective the vaccines are.

And as has been pointed out several times, it's very hard to disentangle humeral immunity from T-cells from natural killer cells from FC effector functions of antibodies. So I don't, I'm not sure that serology is the only issue. I think we really need to look at rates of disease. And I think it's important for the CDC to continue to provide evidence regarding deaths and hospitalizations that are truly caused by COVID-19 rather than just associated with hospitalization. So I just, I would be careful about placing too much emphasis on serology. Over.

Dr. Perlman: Okay. Thank you. Dr. Bernstein.

Dr. Bernstein: Thanks. Can you hear me?

Dr. Perlman: Yes.

Dr. Bernstein: Oh, great. Okay. Thanks. So, I believe we still need to vaccinate the unvaccinated. And so anything that results in better public communication would be extremely valuable. That being said, and this has been brought up by others in the course of the day, is how should outcome expectations be prioritized for the Covid vaccine program in making these kinds of decisions? Realistically, I don't think we can have it all. Less infection, less transmission, less severe disease, and less long Covid. And that seems to be a major challenge for public messaging. So I was wondering how we prioritize for the program.

Dr. Perlman: Yeah. So one thing is, this sounds like this is an important point. This part of the session, I think we should concentrate on the vaccine composition. I don't know if you, do you, is your comment relevant for that?

Dr. Bernstein: Well, I think, well, if we were going to, — I'm not clear that using a bivalent in the younger pediatric age group makes the most sense. But we can talk about it later if you don't think it's relevant.

Dr. Perlman: Yeah, yeah. I don't, it's hard for me to know. Dr. Offit?

Dr. Offit: Right. Thank you. So I certainly support this, would support this. The reason I would support it is I do think it's important to get closer to the strains that are circulating for certain groups. So, I mean, right now, BA.4 is gone. BA.5 probably represents less than 5% of what is circulating, but certainly a lot closer than Wuhan is. And I think for the goal is to keep

people out of the hospital. That's the goal, you know, to not overwhelm hospitals. And I think for some people who are so medically frail that a mild infection could land them in the hospital. So I think it is important to try and get closer to the strains that are circulating. I agree with that.

I also think that, that when we talk about those high risk groups, whether it's people who have multiple comorbidities or people who are elderly or people who are immune compromised, there are a number of those people who aren't going to make a good immune response. I mean, I just had my 94-year-old mother receive a booster dose. I think she's probably not making a very good immune response. And I do think we, we should always, always make the point about giving antivirals, and hopefully there's an oral form of Remdesivir that's around the corner. That'll be good.

But, and then the second issue in turn is, is protecting against severe disease for just the general population. I think we already have that vaccine in the Wuhan one strain. And any of those would work. Because, again, I think T-cells are important. And there were a number of researchers like, you know, Jerry Weir and Alessandro Setti and, and Daniela Weiss Coffee at Scripps, and John Weir at our place at Penn, who I think have made it fairly clear that there's a role for T-cells in that. And there, it's like win-win, which is, so there, I don't — that does not fit the flu model for me. So, vaccinating everybody every year as to thing from flu where you really do need to be strain specific. I mean, when we miss, and we've missed on H3N2, a miss is a mile. And if we miss with the vaccine strain and people get the vaccine and it doesn't match the circulating strain, you have pretty much no protection, whereas that's not true with this virus. As Dr. McInnes said, I mean, this isn't flu and you do still have protection against severe disease, But I think we need to define what we want from this vaccine. But I certainly support this this voting question the way it's written. Thank you.

Dr. Perlman: Okay. Thank you. Dr. Sawyer.

Dr. Sawyer: I, too, support this idea of harmonizing the composition. The voting question doesn't include a timeframe. I do have some anxiety about the amount of data in under two-year-olds with a primary series with bivalent doses. It sounded like Pfizer had 90 patients, and Moderna presented a little data on a similarly small number. So I guess my question is for FDA, how much data do we need to recommend a bivalent primary series for young children?

Dr. Perlman: Does someone from the FDA want to address that?

Dr. Marks: Sorry about that delay. So thanks for that question. I think we'll be looking at the totality of the data that we have. Some of the data from the mRNA vaccine is mutually reinforcing in terms of helping us in terms of numbers. We agree that the numbers right now are small. Hopefully as additional data come in, we will have a larger data set in this in this age range. I think the reassuring thing, though, has been the safety profile that we have seen with the bivalent booster. It mirrors very well the original vaccine in this age range. So again, we, this is like a lot of the questions we've had today. The answer is we will need more data. We obviously care about the safety first and foremost in this age range. But I think, ultimately, the overall thought here is that getting towards one vaccine composition for everyone will ultimately be much, much more helpful. And it also avoids exposing the youngest children to antigens that don't really exist in the real world anymore.

Dr. Sawyer: Thanks.

Dr. Perlman: Dr. Berger.

Dr. Berger: Hi. Thanks. I obviously, overall, I think I agree. Couple to do with Dr. Offit here. I think our job here is really to protect against severe disease. And, you know, I think what we

heard this morning was 16 times lower risk of hospitalization, 13 times lower risk of death when you're comparing unvaccinated. It really makes a difference if you can actually have a strain that's matched to the currently circulating strains themselves. And what we're trying to do is really offer that best protection possible, and I think it makes sense to simplify this process, have a single composition. I do think that there are questions still that remain unanswered, such as dosage amounts, especially in the pediatric populations, as we were just discussing. You know, I'm supportive of the question itself. I think the only thing that — I kind of wish it stopped at that single composition and didn't give the, for example, I understand that's the currently, you know, current composition would be this bivalent version, but we already know that those strains are actually circulating out.

So I think there are still questions about whether the original strain, the Wuhan strain, would need to be included in that. Certainly BA.4 and BA.5 are questions, whether we should be switching over to different ones at this point. I think all that remains to be said were to be determined, but overall I think movement towards a single composition makes sense to simplify this process. That's all.

Dr. Perlman: Okay. Thank you. Dr. McInnes.

Dr. McInnes: I'm going to, I had originally four questions. One I've already addressed to Jerry, so I'm moving to number three. And I think our challenge here is, you know, have the bivalent boosters added any data to the monovalent? I think that's sort of something that we have failed to articulate. Obviously, BA.5 is closer to Wuhan. So where are all this noise coming from? So I think we don't have randomized comparisons to demonstrate protection against severe disease, and I think it's a really problematic message for the community. I am not a public health vaccine person, but you know, I give the little example of two adult children who are both musicians,

four vaccines. They move to a Nashville, they go out one night, and three days later, they're symptom symptomatic. And they were pretty sick. And one of those was a bivalent booster. So all I can say to them is, well, imagine how sick you would've got if you hadn't had these vaccines. And that's not a great message to try to deliver. So I believe we should move from this, what was the circulating strain, to a more contemporary strain. But you may still get reinfected. So I think that is a real challenge. And the message says that you would've gotten more sick and landed in the hospital. You know, it resonates with me, but I'm not sure it resonates with the recipients of the disease. Thank you.

Dr. Perlman: Okay. Thank you. Dr. Gans.

Dr. Gans: Thanks so much. I think part of the issue that people are having with this is vaccine composition. That's a big issue that everyone has raised multiple issues related, and I think we'll be dealt with in the questions and how we pick which particular strain would be in an upcoming vaccine. I think this question really should be vaccine harmonization. And in that, I think there's a lot of agreement that what we need to do here is really think about how we're moving until we get to that next stage. So what are we doing for the primary, would be the same as what we're recommending for the booster. And I completely agree with that. And I do think it is important for us to realize that, you know, everyone talks about death and severe disease. I mean, maybe this is going to be included in severe disease as the primary outcomes, but I have to tell you, we're seeing more and more children with coinfections, with Covid plus Covid, and they're definitely more severe than if they had either or. And so I do think the protection is broader than what people are identifying as the only marker. There is definitely disease that is happening as a result of infection with these viruses, and particularly in our youngest children. And so I agree that we have to get closest to what is circulating. The ones we have right now are

the examples that have been laid out here. And so I would support this. And I just think we're confusing people by saying composition and not harmonization, and then therefore we can move on to the next discussion. Thank you.

Dr. Perlman: Thank you. Dr. Wharton.

Dr. Wharton: Yes, thank you. I am supportive of this question. I do think there's some data gaps that it will be good to get more information on. I'm glad that there's more information expected about optimal dosage for children. And there's some questions about different dosages for, say, the primary series and booster for the Moderna vaccine for adults. There's some unanswered questions, some things to work out, but I think this is absolutely the right thing to do for the program. It will make things simpler. I know how we ended up this way, but I think this is a good decision to make, and I'm supportive of it.

Dr. Perlman: Okay. Thank you. Dr. Cohn.

Dr. Cohn: Thank you. I'll just echo what Dr. Wharton just said. I think this is a very good decision to move forward with this from a programmatic perspective and from an implementation perspective. I just, I would be remiss to not acknowledge that the most concerning data point that I saw this whole day was that extremely low vaccination coverage in six months to two years of age, and also two years to four years of age. So we have to do much, much better. And anything we can do from a simplification perspective, from an optimization of those doses in the future, we're just going to have more kids aging into this age group and needing to be vaccinated. And we really just have to focus on getting those kids vaccinated.

Dr. Perlman: Okay. Thank you. Dr. Hawkins.

Dr. Hawkins: Yes, thank you. So I support this approach. I think vaccine effectiveness is confirmed. Vaccine safety is confirmed, notwithstanding discussions about pericarditis, myocarditis and the need for some not so common things that occur. The average US consumer, vaccinated or not, has accepted COVID-19 is going to be with us for a while. Most, I believe, are hopeful that science will possibly affect the trajectory of this condition, and they want us to be successful. Many consumers are accepting of the annual influenza vaccine. I think that having variability in multiple vaccine administrations, such as multiple Covid boosters, might lead to more vaccine hesitancy, vaccine fatigue. And we're concerned about FDA reliability of CDC reliability. I'm not a researcher, but finally I would reemphasize previous comments about the need for processes and protocols to fill the knowledge gap to help us make better decisions about next steps.

Dr. Perlman: Thank you. Dr. Gellin.

Dr. Gellin: Oh, my camera's still not working. Thanks. So we can't keep doing what we're doing, so we have to move on. It's been articulated in every one of these meetings that despite how good these vaccines are, we need better vaccines. And thank you, John, for a great presentation about some of that pathway to get there. I think this is a reasonable approach. We have to keep reminding ourselves this is not influenza, and we need to keep paying attention to that to make sure that we don't just follow that dogma because we're used to doing it. And that as we move in, this is, we'll try this, this time. I don't think we're setting it in stone, and we'll see how it goes. We may need to adjust along the way. But overall, I think this is a good path forward.

Dr. Perlman: Okay. Thank you. Dr. McInnes.

Dr. McInnes: Dan, are you going to have discussion after the vote or all the discussion before?

Dr. Perlman: No, we're going to have the vote. Then we'll have a discussion about the vote, and then we'll have another discussion about —

Dr. McInnes: All right. I have nothing to say. Thank you.

Dr. Perlman: Okay. So at this point with, I think we've ended our discussion, and I'm going to briefly turn this over to Dr. Paydar to describe the voting process.

Dr. Paydar: Great, thank you, Dr. Perlman. Only our 10 regular members and 11 temporary voting members, a total of 21, will be voting in today's meeting with regards to the voting process. Dr. Perlman will read the final voting question for the record, and afterwards, I'll ask all regular voting members to cast their votes by selecting one of the three voting options, which include yes, no, or abstain. You'll have one minute to cast your vote after the question is read. Please note that once you've cast your vote, you may change your vote within the one-minute timeframe. I'll announce when the voting poll has closed. At that point, all votes will be considered final. Once all the votes have been tallied, we'll broadcast your results and read the individual votes aloud for the public record. Does anyone have any questions related to the voting process before we begin? Okay. If there are no questions, I'll ask Dr. Perlman to please go ahead and read the voting question one more time for the record.

Dr. Perlman: So the question is, does the committee recommend harmonizing the vaccine strain composition of primary series and booster doses in the US to a single composition? For example, the composition of all vaccines administered currently would be a bivalent vaccine original strain plus Omicron BA.4/BA.5.

Dr. McInnes: And I'm sorry. Is there an ‘and’ missing here?

Dr. Perlman: Where?

Dr. McInnes: After primary series ‘and’ booster doses. I don't see that on my screen.

Dr. Paydar: Oh. That's probably because you have probably raise hand block open on your right-hand side.

Dr. McInnes: I don't care. As long as there's an ‘and’ there, I'm okay. Thank you.

Dr. Paydar: Yes. There is an end there.

Dr. Atreya: Sussan, this is Praba. Do you want to talk about moving members from —

Dr. Paydar: Yes, I was just about to do that, Praba. Thank you. Thank you. Sure. Thank you so much for the reminder. At this point, now that the voting question has been read by Dr. Perlman, what we will do, we will move all the voting members and the DFO. Everyone will stay in the room. Everyone who's not voting will be moving out of the room. And please just stay put. Do not disconnect from your Zooms. Stay patient with us for two to four minutes while we conduct the votes and we come back. And at that point I'll read the votes aloud for everyone to see. So non-voting members, you will be transitioning to another room. Thank you. Derek, please let me know when all the voting members are present.

Vote Results

Dr. Paydar: Is everything ready for display?

Derek Bonner:Yes, it is.

Dr. Paydar: Okay. Okay, so we have a unanimous vote, 21 out of 21 voted yes. I'm going to read one by one for the public record. If we could have the Excel. Great, thank you Derek. I'm going to read from top to bottom, it's not alphabetically organized, here we go. Dr. Hayley Gans, yes. Dr. Amanda Cohn, yes. Dr. Mark Sawyer, yes. Dr. Ofer Levy, yes. Dr. Steve Pergam, yes. Dr. Paul Offit. Dr. Stanley Perlman, yes, Dr. Mike Nelson, yes. Dr. Archana Chatterjee, yes. Dr. Bruce Gellin, yes. Dr. Pamela McInnis, yes. Dr. Randy Hawkins, yes. Dr. Adam Berger. yes. Dr. Cody Meissner, yes. Dr. Jeannette Lee, yes. Dr. David Kim, yes. Dr. Melinda Wharton, yes. Dr. Arthur Reingold, yes. Dr. Henry Bernstein, yes. Dr. James Hildreth, yes. And finally, Dr. Eric Rubin, yes. Thanks everyone for your patience as I read.

This concludes the voting portion for today's meeting, and now I'll hand the meeting back over to Dr. Perlman for asking the committee for their voting explanation. Thanks so much everyone.

Voting Explanation

Dr. Perlman: So the next component of this is we go to, I ask everyone on the panel why they voted the way they did, given that we've already had great discussion about this and lots of positive feedback. This doesn't have to be long, so I'm going to do this in alphabetical order. So that means that Dr. Bernstein, you start, and if your explanation, you think you've said it already, you can say, "I've said it already", or say what you want.

Dr. Paydar: Perhaps he's muted.

Unknow Speaker: Does he still have to speak up?

Dr. Bernstein: I'm sorry, I thought you were doing Dr. Berger.

Dr. Perlman: Oh, no, he lost out by one letter there, but you're first.

Dr. Bernstein: Okay. Yeah, I mentioned it before. I think anything that results in a better public communication to get more of the unvaccinated would be extremely valuable. I still have some questions, but I think this is the right direction.

Dr. Perlman: Okay, so Dr. Berger, you actually should have been first, and I apologize to Dr. Bernstein for that.

Dr. Bernstein: Oh, sorry.

Dr. Berger: Sorry. I thought you had called out Dr. Bernstein, so I was not responding either.

Dr. Perlman: Yeah. Yeah, I did. It was my mistake.

Dr. Berger: It's the same rationale that I gave before. I think, as Dr. Bernstein just noted, we are looking to try and get a better vaccination rate here and trying to make this simplified in the process. The information that we heard early this morning again 16 times lower hospitalization, 13 times lower death against compared to those that are unvaccinated. I think those numbers speak for itself. So I'm definitely supportive of simplifying the process, harmonizing the vaccine composition between primary and boosters.

Dr. Perlman: Dr. Chatterjee.

Dr. Chatterjee:Thank you Dr. Perlman. Speaking with colleagues, friends, family, questions I'm answering from the community, there's so much confusion about these different formulations that I think anything we can do to ease up on that confusion and simplify things it's going to be a

good thing. I concur with my other colleagues that there definitely remains a need for these vaccines and for us to do our best to get them into arms.

Having vaccines is not sufficient. We need to have them be used. And I voted yes because I think this is a step in the right direction and getting us there.

Dr. Perlman: Dr. Gans.

Dr. Gans: Thank you. I stated some of my thought process earlier and so I'm not going to repeat those. I continue to believe that the one thing that I do think it's important to state is this isn't only a convenience thing to increase the number of people who are vaccinated, which I agree with my colleagues is extremely important for all the evidence that was related. But I also think moving towards the strains that are circulating is very important. So I would say that the science also supports this move. And you do see, I know there's a lot of controversy about this, but it does seem that much of the data points, in the same direction as Dr. Weir says, that these are additive, and I think hopefully will help people get on board.

Dr. Perlman: Dr. Kim.

Dr. Kim: Thank you, I am totally convinced that the bivalent vaccine is beneficial as primary series and its boosters. Furthermore, the updated vaccine safety data are really encouraging so far. And I'll add that that low coverage rates for infants and toddlers and as well as adolescents, young adults, and even older young adults is very concerning. And it's clear that we should not continue the path that we've taken thus far. So if clinicians and pharmacists have to use flow diagrams and other helpful items like posters and such to understand which vaccines they should give for whom, and when the public's response really shouldn't be a surprise. So I enthusiastically support this recommendation. Thank you.

Dr. Perlman: Okay. Thank you. I, Dr. Cohn, I think – did I cut you off?

Dr. Cohn: Great. Thank you so much. I just wanted to – I am totally in agreement, but I did just want to make the comment that I don't want to forget that we also saw data that the monovalent primary series was working quite well against infection or symptomatic infection in younger children. And so there will be a period of time where there won't be bivalent primary series available. That will take some time, I assume. And I just think that we need to be clear that people should still continue to get vaccinated and not wait for these bivalent primary series products.

Dr. Perlman: Okay. Thank you. Dr. Offit.

Dr. Offit: I agree with everything that my committee members just said. Thank you.

Dr. Perlman: Okay, Dr. Pergam.

Dr. Pergam: It gets hard to add to comments that people have made, but I'll just reiterate that clarifying, making the process simpler for the community is going to be critical, and I think there's real value in that. It also feels. And indicates better from the data than, we're choosing strains that are a little more relevant to what, seeing the community, and I think there's real value in that. So I'll be really curious about the next stage discussion about choosing the specific. So I'm really looking forward to that component of it because I think that is actually what warrants further discussion.

Dr. Perlman: Okay. Thank you. And I'm next and I don't have anything to add to the discussion. Dr. Rubin.

Dr. Rubin: Nothing to add.

Dr. Perlman: Okay, so now we're going to go to Dr. Gellin.

Dr. Gellin: Yeah, thanks. On top of the few comments I had before I think that this is, we're at a pivot point and I think this is an opportunity as we make this move to really evaluate every part of this and make sure that all the assumptions that went into this are the right ones.

And while I have the microphone, my vaccine card, I'm out of lines, and so maybe the other the other pivot point is to try to figure out how we get into the information age rather than carrying around these little pieces of paper that we hope we don't lose.

Dr. Perlman: Amen. Dr. Hawkins.

Dr. Hawkins: Yes. Thanks for the opportunity and I have nothing else to add to my original comments,

Dr. Perlman: Dr. Hildreth.

Dr. Hildreth: Thank you, Dr. Perlman. I agree with the approach that's being taken here. There's a lot of disharmony in the public about these vaccines. They're very confused about all the formulations and different manufacturers, so hopefully this will solve some of that. I hope we can get a better job of vaccinating children. I think that's a big concern. And I also want to point out that the impression one gets from listening to these meetings is that we're focusing on mRNA vaccines when another vax recombinant protein vaccine is an excellent one as well and should be part of our conversation. Thank you.

Dr. Perlman: Thank you. Dr. Lee.

Dr. Lee: I don't have anything to add to what's been said. Thank you.

Dr. Perlman: Dr. Levy.

Dr. Levy: As we've turned the corner from a pandemic phase to an endemic phase, today's vote marks a big practical win for the American people. This is going to really simplify things, benefit public health. There's more work ahead as we discuss today, but this will be a big win. Thanks.

Dr. Perlman: Thank you, Dr. McInnis.

Dr. McInnes: Here we go. I had four points. I addressed the first, which was to the FDA, was that Covid is not flu. I addressed the third and the fourth, which is you have a bivalent, are there any data to suggest it's better than monovalent as a booster? And secondly, we really don't have – what's the public messaging around us. I took all these vaccines, I still got sick.

But I have a second point that I want to just bring up is that this whole conversation is very much mRNA focused. And I think Dr. Hildreth brought this up just like 30 seconds ago. I'm concerned about that because, I've been in that area for a very long time, and it's like first to market gets the place and I get it, I understand how that works, but it may not be the best for what we're thinking about either as priming or as boosting. So I want to urge making place for other platforms. [indiscernible] has been fantastic, they can produce it really quickly. But it may not give us the breadth of coverage, which is really what I think our problem is right now. We know we induce really good neutralizing antibody with mRNA vaccines, but it seems to be pretty short lived. We can boost it again, and then again, it seems to be pretty short life, or lived, however you want to pronounce it, and so I want to be sure we don't shut down other platforms in trying to achieve what is the best approach on either an individual or a population basis. Thank you.

Dr. Perlman: So did you have a comment on the vote?

Dr. McInnis: I voted yes because I thought that was my comment.

Dr. Perlman: Oh, okay. It was just why you voted the way you did. Okay.

Dr. McInnis: Yes.

Dr. Perlman: Thank you. Dr. Meissner.

Dr. Meissner: Thank you, Dr. Perlman, and I voted yes because I think it's very hard to predict the evolution of this virus. I think that it, we can say that new sequences will appear on a regular basis, and I, any assessment of vaccine efficacy is really a snapshot in time based on the circulating variants and background immunity that comes from vaccines or infection or both. So I think having a bivalent vaccine is reasonable and I think it should be standardized. And I also agree with Dr. Hildreth and Dr. McInnes, I think it's important for the protein platform to continue to be available because we don't fully understand yet all the advantages and disadvantages of different vaccines. But it's important to have more than one platform.

Dr. Perlman: Okay. Thank you, Dr. Nelson.

Dr. Nelson: Thank you. Fully supportive, certainly voted yes. Simpler is better. And frankly, I think we saw great evidence today that closer is better, even when the strain that's actually in the vaccine is long disappeared or on its way out. It had relieved my fears that we would be in this game of trying to chase the latest and greatest, and we saw reassuring data today that says, just getting closer gives us some additional benefit. I'm hoping that the momentum of this simplification and this additional efficacy and safety data will spur additional vaccination acceptance at all age groups. Thank you.

Dr. Perlman: Thank you, Dr. Reingold.

Dr. Reingold: I agree with Dr. Offit.

Dr. Perlman: Okay. Thank you, Dr. Sawyer.

Dr. Sawyer: My rationale is the same as Dr. Nelson, bivalent is better, simple is better.

Dr. Perlman: Thank you. And Dr. Wharton.

Dr. Wharton: Thank you. No additional comments.

Topic One

Dr. Perlman: Okay. Thank you. Okay, so now we're going to move on to the two discussion topics. Can we put those up on the screen again? Okay, so these two discussion topics are the first one which we'll discuss first is simplification of COVID-19 Vaccine Use Immunization Schedule. Please discuss and provide input on simplifying the immunization schedule to authorize or approve a two-dose series in certain young children and in older adults and people with compromised immunity and one dose in all other individuals. So we're going to discuss that first and then we'll read the second one in a bit of time and we'll discuss that one. So do I have comments on this one, Dr. Rubin.

Dr. Rubin: Thank you. A question and a comment. The first, the question is for those who have never been infected or vaccinated, we would not give a priming dose, that's the idea here, that we would give a single dose? And that, that does seem, we do have data for that, and it does suggest that a two-dose series is better. I'm not sure if that's what that means here. And it seems like everyone who has not been vaccinated and doesn't have a good record of infection should

require two doses. Otherwise, I think it's okay. But I just want to point out how little we know. We know nothing really about dosing intervals and how that affects the immunity that we get and or protection, a more important protection that we get. And I would think that we really want to be doing those studies. It's very important to collect those data. It can be collected as part – of course, we have to make decisions. The FDA has to decide what the dosing interval's going to be, but I think it's very important to, in advance, decide what kind of data should be collected so that we could understand if we're doing the right thing.

Dr. Perlman: Thank you. I think, Dr. Marks, did you want to respond to that?

Dr. Marks: No, I didn't want to respond. I just wanted to make a correction here. We meant to – we don't mean to limit you to thinking about a two-dose series. We wanted to just note that a multiple dose series with an example. It could be two doses, and some might have questions about whether it would be more than that in in those with compromised immunity. I think the major issue is, the concept was, if you've had documented COVID-19 or if you've been vaccinated previously, you would just need one dose versus others who might have multiple doses. Thanks.

Dr. Perlman: Okay. Thank you. Dr. Gans.

Dr. Gans: Thank you. Yeah, I was looking at this because of the way that it was phrased to us is, this is in previously immune individuals and so this, I think is getting at, do we need to continue to need "boosters" and what would be the timing of that? And I think that we have raised over this meeting time, but I think since we're discussing, it's important to bring it right here. This is going to be a probably different discussion for different groups as is outlined there. So I think we need age-specific information and underlying condition specific information. And

this leads into persistence. We're in a completely different place than we were originally when we needed to get our population community boosting and immune, I'm sorry, immune and that related to how many doses that we need. I also think those people who continue to be naive year to year will obviously need a different schedule, and I'm not sure that two doses – that's the way it was studied, that's the way we accepted it, but we saw that we did need a boost, and I'm not sure that isn't the right way to do prime, prime boosts like many naive people need coming into a new season. So I think we're in a very different place. We have a lot of population immunity and I think we need persistent studies to answer this question. And I think those need to include broad immunogenicity studies that's been outlined, T-cell, B-cell mucosal with combined with efficacy data and persistent data. Now that people are immune, how long does that all last? So, I think that's what – if we're going to ask companies for, that's what I think we need, and look at naive versus immune.

Dr. Perlman: Thank you. Dr. Chatterjee.

Dr. Chatterjee:Thank you, Dr. Perlman. I would echo Hayley's comments but also add that as we look at this question, particularly for the young children We would at least, I would want to see a lot more data. The numbers are just too few for us to really make scientifically sound decisions regarding this question. So the trial data needs to be much more robust than we have seen in the past. As one of our colleagues pointed out, we have entered into an endemic phase. This gives us an opportunity, a window to really go back to the drawing board, if you will and look at the science a lot more closely than we were able to do in the face of a deadly pandemic, which we were facing two years ago.

Dr. Perlman: Thank you. Dr. Wharton.

Dr. Wharton: So given where we are with the vast majority of the US population, having been vaccinated and many individuals having had Covid, and many people have had both vaccine and Covid. It does feel like doing a reset for our vaccine recommendations so that for many people, regardless of what they got before a single dose really does make sense. There's already – it's already been raised that there's a lot of uncertainty for what are the exceptions. I do think there will need to be some careful looking at, again, dosage and number of doses and dosage in young children so that we get good protection in that vulnerable population. And thinking about what is needed to protect other, at-risk groups. But I think in general this is a good move to make at this point. It might not be forever. We may end up revisiting this relatively soon, but I think for the next step for where we are it feels to me like this is the right thing to do.

Dr. Perlman: Okay. Thank you. Dr. Sawyer.

Dr. Sawyer: I certainly support this approach. Simpler is better, as I've stated. Pediatricians are used to adjusting the number of doses of vaccines based on age, which is likely to be one thing we conclude, as well as high risk populations, specifically immunocompromised patients. So I think this is definitely the way to go as soon as we can figure out how to do it.

Dr. Perlman: Thank you, Dr. Marks.

Dr. Marks: Sorry, that was an error of a hand up. Sorry about that.

Dr. Perlman: Oh, okay. Dr. Offit.

Dr. Offit: Thank you. I just want to underline what Dr. Gans just said. I think certain things are clear. This virus is going to be with us for years, if not decades, and there will always be vulnerable groups who are going to be hospitalized and killed by this virus. I think we need two pieces of information from two different groups. One is we need the CDC to tell us exactly who

it is that's getting hospitalized and dying from this virus. What are their ages? What are specifically are their comorbidities, if they're immune compromised? In what manner are they immune compromised? Did they recently get a vaccine? Were they treated with antivirals, et cetera. And that has to be provided in concert with immunological data, presumably from academic immunologists, as to what exactly are the immunological predictors, not just antibodies, but also cellular immunity for who is at risk. Then, and only then, can we really best make the decision. Who gets vaccinated with what and when. Thank you.

Dr. Perlman: Thank you. Dr. Pergam.

Dr. Pergam: Yeah, I just want to come back to a question about P's again is that the confusion still exists because there's two different formulations with the, a different number of vaccines that are given. And as we're thinking about this process, we need to bring the two different forms of vaccine platforms that are being used, but also as we're discussing this it's been brought up a couple times, but I think we also need to keep in mind how we are going to sort of approach this question when it comes to other vaccine platforms, because it may not be exactly the same how we approach each of these.

Dr. Perlman: Okay. Thank you. Dr. Reingold.

Dr. Reingold: Yeah. I want to go back to a point that was made earlier, or a couple people have made, about whether these vaccines are intended to prevent infection or not. I can't tell you how much time I spend trying to disabuse people of the notion that if a vaccine doesn't prevent infection, it's not a vaccine. I point to tetanus is a good example of a vaccine that does a pretty good job of preventing disease without preventing infection, and there are certainly others. And

similarly that the overwhelming majority of kids who get infected with poliovirus or measles virus do just fine.

Nevertheless, we think it's pretty important to prevent even those rare, serious outcomes by vaccinating everybody. And so I think the public health messaging here really does need to be much better than it's been in the past. That what we're about is, I think Dr. Ross said before is preventing serious illness, hospitalization, and death. And that's really what we should be talking about with these vaccines. Thank you.

Dr. Perlman: Thank you. Dr. Gans.

Dr. Gans: Yeah, sorry for coming back around, I realized that I was negligent in not bringing up the other piece of information. It's probably obvious that we need, but we really need to make a plea that in order also to answer this question of how often and along with the immunogenicity and the efficacy data is safety data. So we heard a lot today about our really rigorous and robust US systems that we use to really look at signals. But I would suggest that there is so much rich global data in the millions of doses that is being given to people. This is an amazing opportunity to collaborate, and I think if nothing else, the pandemic has taught us that kind of collaboration is really necessary and is important for the sharing of information. So I would say as we're making these decisions, the other piece of data that I would like to see is the robust safety data reported.

Dr. Marks: So this is Peter Marks. Dr. Gans, this actually I can answer for you and Dr. Forshee can help as well. During the pandemic we have been working with a network through the International Conference of Medicine Regulators as about 60 countries that have been exchanging pharmacovigilance information. And that's why when a safety signal comes up, we

can actually query the other countries. And it was very reassuring with this late latest stroke question that this was not seen in in millions of doses given overseas. I couldn't agree with you more that this is a fantastic opportunity to collaborate with various other regulators to be able to put together the maximum amount of safety information that we can.

Dr. Gans: Thanks.

Dr. Perlman: Thank you. Dr. Meissner.

Dr. Meissner: Thank you, Dr. Perlman. One question that may arise is the issue of interchangeability of these vaccines once they're standardized. And the issue for both pediatrics and for older individuals including adults, is going to be mixing messenger RNA vaccines and mixing platforms. And we do have some information about heterogeneous immunizations, but that's something that the FDA may want to consider. Over.

Dr. Perlman: Thank you. So I – Dr. Reingold, did you have another comment?

Dr. Reingold: Sorry.

Dr. Perlman: Okay, so if there's no more comments on this question, I'll just briefly try to summarize what I've heard and then we'll move on to the second discussion topic. So I think everybody thought this was a good idea to simplify the schedule and to use either this multi-dose series in young children, it says two, but maybe two won't be adequate, we have to get more data on that. And then, and same thing in older adults and people with compromised immunity. I think there's, the idea of simplification is good. I think we need more data. I think my general feeling from the committee is that we need more data to figure out exactly who should get the two-dose schedule, who should get the one. Particularly, as it was mentioned earlier in the day, how even for immunocompromised people, there's different vulnerabilities. Some people never

responding and other people responding almost normally. So all that kind of information will help determine this immunization schedule. But in general principle, the committee was supportive of going forward with this.

Dr. McInnes: Stanley, can we add one thing please?

Dr. Perlman: Sure.

Dr. McInnes: I think we made the mention that this particular platform, that the mRNA may not be the best. I don't know, it could be, but that we should leave space for other approaches for both priming and boosting.

Dr. Perlman: Yes, and I think that's what we're going to discuss next.

Dr. McInnis: Thank you. I'm sorry, it's just I don't want to close the door on it.

Dr. Marks: Yeah. Just so you know, we hear that loud and clear and in fact, part of the idea of harmonizing things here is to hopefully engage other sponsors to come in and have a variety of different platforms that might be able to be used. And we also are obviously looking forward to seeing potential platforms come in that might be improvements on the current generation of vaccines. Over.

Dr. Perlman: Dr. Berger, did you want to say something before we moved on to the second question?

Dr. Berger: Yeah. Thanks, Dr. Perlman, and I just wanted to add one piece to your really great summary there, which is just, we also need data on dosage, not just the number of doses and who gets them, but also the dosage to be given.

Topic Two

Dr. Perlman: Okay. Yeah. So that should be added. Okay. Okay, so if we we're, if we're satisfied with this question, or at least for today, let's move on to the second question, which is vaccine composition. So we are asked to discuss and provide data input on the consideration of periodic updates to COVID-19 vaccine composition according to the currently authorized or approved vaccines to be available for the use in the fall of 2023. And I think based on our previous discussions today, we can make this a more broad discussion of what we think about vaccine compositions whether it be mix and matching or protein versus RNA. So just a general discussion over the next bits of time. Dr. Chatterjee.

Dr. Chatterjee:Thank you, Dr. Perlman. Yes, on this question I think it is critically important that we pay attention to the epidemiology and what is happening with the emerging variants, how the vaccines are continuing to hold up against them. We've had much discussion today about not wanting to chase variants, and I agree with, but on the other hand, we do have to be mindful and pay attention to make sure that the vaccines continue to be effective.

I thought that the discussion around the timing of any proposed changes, it was interesting. The late spring versus early summer timeframe seemed to be something that, at least the three vaccine manufacturers that were part of our discussion today, seemed to indicate that they would be able to provide the formulations and manufacture in time what we would need for the fall. So I think this is like everything else with this virus, it's a virus and evolution and we have to respond accordingly, as it changes and as we see changes happening in its epidemiology, and in the epidemiology of this disease over time.

Dr. Perlman: Thank you. Dr. Rubin.

Dr. Rubin: I'm also going to be supportive, as Dr. Chatterjee is. We don't know what's going to happen. I think there is evidence that we've seen that there is at least a slight advantage for the omicron, the better match to omicron strains that we're using now are antigens that we're using now. And it may be a bigger bang for our buck, for the buck, as these variants become more and more distant, which is certainly what's going on right now with the XBB strains and the other VA2s. I think we want to do it, and we're not going to know how often to do it. I think it's quite reasonable to think about another one for the fall. I think that's a very good idea and there is a limit to how often we can change, but I think that for step one, that would be okay. It's hard to say that it's going to be annual at this point.

Dr. Perlman: Okay. Thank you. Dr. Gans.

Dr. Gans: Thank you. So I think relevant to this conversation, however of course it's highly embedded with the others is going to be – when I think of composition I also think as we're coming, as was expressed by my colleagues, as we're coming out of a pandemic, we have a moment to step back and think about composition more broadly. I would definitely agree that we have to understand how the drift, shift of these variants is going to impact what our current immunity is towards them and how efficacious that is in preventing the severe outcomes that we're all worried about.

And so again, that gets embedded in understanding the correlates of protection, which we can't again emphasize enough. But it also relates to, and I think I did pose this question to our vaccine manufacturers, to go back and look at the dosing. So we know that we were all thinking

about trying to get something out into the market to protect those who are naive, but we have a chance to re-look at that and really understand that.

So I would really make that plea particularly in the pediatric populations where that is more – pediatric populations also are immunocompromised, so maybe the idea is not more doses, but a higher dosing like we do with the flu vaccine for our elderly. So really looking at different strategies for individuals who maybe don't get the same immunogenicity from just a routine, so not one size fits all, but again, these banks of preclinical understanding as these companies are looking at the different vaccine, the variants of concern to understand if we really need to change or if there's actually protection broadly. And so that would be my plea for this particular question, but I do think we're going to be entertaining this at some cadence, which in the future may be different than it is now.

Dr. Perlman: Dr. Pergam.

Dr. Pergam: Yeah, so I, I think it's interesting, this concept of flu being the once-a-year sort of approach, maybe it'll work, but I guess my hesitation about that is if you look at the past three years, there's been at least two of those years where there's been a large uptick. It was Delta one year, and I can't remember exactly what strain it was more recently where we've had these summer increases that have been important as well. And while we can't, as we said, we can't be chasing strains, we can't be doing that. I wonder if initially there may be some value in thinking about meeting and discussing this at different time points at least those initial few years while we sort through this because it feels like we're planning for the future without really knowledge based on a couple of years. And I'm not sure that we have enough data to say exactly when we should be making these decisions just as a point.

And then secondarily, I think one of the biggest questions that we're going to have to think about and I know this will be discussed in later discussions, is do we include the primary strain or the Wuhan strain in future vaccines? I think that's a real big question we're going to have to debate and evaluate in our plans for future vaccines.

Dr. Perlman: Good. Thank you. Dr. McInnes.

Dr. McInnes: Thank you. So, thank you very much. I'm struck about being left with an approach that really works very well, mRNA with high efficacy for a short period of time, and I'm struck by falling asleep at night thinking about B-cells, and clonal expansion, and what anybody I'm in contact with needs in order to provide protection against an incoming antigen. So I'm struck by that we've leapfrogged over the data that we normally have, which is dose response against antigen put into the system in a readout. And I'm struck by our ongoing, lingering about T-cell and mucosal responses, which I wish after 30 years we knew more about.

I'm very convinced we need from a public health perspective, even though I would never hold up my credentials against public health people, is that we need broader protection. We seem to be in a very narrow tunnel here about highly specific protection for a short period of time, but I'm not sure how much broad protection we are left with after having received a full primary series and or a booster. And that bothers me because in the long run you're going to be chasing this virus. I don't want to chase this virus. So I think I would make a plea for ongoing rivet driven research, not slow-paced back seat research on broader protection. And that may be a different platform, it may be a different approach, I don’t know, but I think we need it because otherwise we're going to land up in the same meeting six months from now.

Surely BA.5 is closer to Wuhan then what we've been dealing with, but I'm still not completely convinced bivalents are giving us added data to the monovalent, I'm still thinking about that. I think it's good to be matching the circulating strain, but I don't want to match the flu model. So I want to fight for a vaccine that has broader protection and not shut the door on that. Thank you.

Dr. Perlman: Thank you, Dr. Gellin.

Dr. Gellin: Thanks for the FDA, I want to understand the second part of the question. I'm assuming that by, based on what we voted on, we're going to be together again in June for the next start of the cadence. So what is this, including the currently authorized for the fall? Does that mean the things that are currently available might be with, regardless of what we do in June, we'll then be potentially in the market for the fall?

Dr. Marks: I think the idea here is that we would anticipate having another VRBPAC meeting sometime in May-ish, the May-ish timeframe to have a discussion of what's circulating and what would make sense to put in the composition of a fall vaccine. Knowing how fast things are moving these days with the variants moving across. That again, it will only be – it's as good a guess as we can make, but that's the right timing that we need to do, to have a meeting in sometime in late May or early June in order to be able to have the manufacturers of the mRNA vaccines have time. And now actually we're going to go back, and we'll talk about what we need to do for the protein-based vaccine. But that's the idea here is that we would, we'd have another meeting and I think the whole idea of this framework would be that for right now, barring some strain comes along that is — essentially breaks out of the T-cell mediated immunity that's providing protection against severe disease in the general population, that we would have – essentially we're proposing at least, I'm not saying just, but at least one meeting per year on this

strain selection and then possibly others obviously, if something comes up, I think that's the model that's being predicted.

And I just want to echo something. We totally agree with everyone, this isn't flu. On the other hand, influenza has served – the model of how influenza strain selection has worked, not to a T, but just the general model has been a very important public health advance. And so we can take the best of that model and then essentially adjust around it. Over.

Dr. Gellin: If I could, maybe for Amanda, is there a companion, [indiscernible] discussion trying to think through how these, particularly around timing, how these are going to be best used given the sort of, the relatively short life of the immune protection. We're trying to think that through, for which populations, assuming vaccines available in September, when should people get theirs? Over.

Dr. Cohn: So I would actually pass that off to Dr. Wharton who's our current ACIP Executive Secretary. But I will say that what Dr. Marks is saying does require that all of these systems that we have in place to do the surveillance, we have to keep those going in order to answer these questions over time. And so I do think this is also an opportunity to just reaffirm that the incredible amount of work that multiple Federal agencies are doing really needs to continue to give us the data that we need in the future.

Dr. Wharton: And we'll continue to work very closely with our colleagues at FDA to try to assure a program that works.

Dr. Perlman: Dr. Nelson.

Dr. Nelson: Just two quick comments as we wind up. One is regarding dose, so I too am very interested in getting very granular data with respect to dose response curves. I think those will be

important for the discussion of composition as we look into multi-valency for these vaccines and the delusional effect that can occur with this type of formulation. We have the historical nature of data for influenza, but I'm not sure we have it for the COVID-19 vaccines. So I think that will help inform our discussion later in the year as you select, not only which strains to put in the vaccine, but exactly how many.

And the second one is an appeal for leaving the window open for availability of these vaccines once they are decided upon and produced for an entire year. We've talked a lot about the parallelism with influenza. My fear is that it would, there would be a shorter window of opportunity for individuals to get this valuable vaccine with unpredictable seasonality at this point. So those who have been unvaccinated and entering windows for primary vaccination or our primary series, if you will, shouldn't be excluded from getting it in the spring or early summer. So I would put that on the table to think about ways how we can communicate that there is still value in getting vaccines outside of the typical influenza window. Over.

Dr. Perlman: Dr. Gans.

Dr. Gans: Just because – it's the issue of, I don't know that June was suggested time for this all to happen actually gives us enough time in case there are still questions that need other information that needs to be gathered. So that concerns me a little bit, and I think this is a landscape that's changing quickly. There's so many things we need to think about that changes – that I would ask for a longer period of time so that if there is additional data we need to make any decisions, it can happen.

Dr. Perlman: Okay. Thank you, Dr. Bernstein.

Dr. Bernstein: Yeah, I agree with the, I want to emphasize what I heard Dr. Nelson say. I think that this, people need to recognize that this pattern is not necessarily the flu, and therefore we may need to meet more than once a year to look for this as a fall vaccine. That it really is necessary to be received more frequently, not more doses, but it is something that may necessarily be important to receive over the summer, for example.

Dr. Perlman: Okay, thank you. So I just wanted to make a couple of comments that weren't made already. So one is in terms of keeping up with the virus, I wonder if we continue, we probably need to continue doing the extensive sequencing of the virus genome that we've been doing. We might be able to get away with just looking at a virus that's isolated, but I think the genome is a great help.

And the second thing is that there is a, there was one bit of precedent here with another coronavirus with 229-E, which when before the pandemic, when I used to teach about this virus, I would tell people that this virus is in variant all around the world and over time it's never changed. But one of the things that came out in 2021 is that in fact, the virus has changed. So that serum from 30 years ago doesn't neutralize the virus that's available now. So, this is relevant I think, because one of the things about keeping the ancestral strain in the vaccine is the question of whether we would go back to that original variant. With 229-E it doesn't seem to have happened, and I think with flu it happens over many years. So this may inform our thinking about whether to include the original Wuhan strain in the vaccine, because maybe we're never going to go back there, so maybe it's not important anyway, something to think about.

Does anyone have any other comments, if not, I'll summarize all the comments that we've had up, up till now. Okay. So I think there's a general agreement that updating the vaccine composition is good and that whether it comes to being once a year or how it actually pans out,

that we need to have as much information as we can. So, we need to have information about how the vaccine is working, and the epidemiology of the vaccine.

We need to keep learning about efficacy. As I just said, as we said in the first discussion point, we need to have more information still about T-cell and B-cell and non-neutralizing antibody responses so that we can really understand what we're doing and the combination of different strategies, whether it be protein based or mucosal based was also something to consider. Probably not for the fall of 2023, but maybe the mixing of the RNA and protein vaccines is something we will need to address then or should address there. So I think that's most of what I would cover. I don't know if anyone wants to add anything to that, if not –

Dr. McInnes: Thank you, Dr. Perlman.

Dr. Perlman: Okay, then I'm going to hand this back to Dr. Paydar.

Closing Comments

Dr. Paydar: Great. Thank you, Dr. Perlman. I would actually like to ask Dr. Marks if he has any comments for disclosing remarks before we adjourn the meeting.

Dr. Marks: Thanks very much. Sorry. We're getting used to having meetings now where there's more than one person in a room, and sorry for the echo that occasionally occurs, apologies for that. First of all, I just want to thank the advisory committee members today's presenters and our advisory committee meeting staff for all of the work that went into this also appreciate all of the public commenters. I do have to do a special shout out both to the FDA staff

who did a wonderful job preparing this briefing book, but also to Dr. Perlman, who has done an outstanding job stepping in at the last minute. And talk about trains departing on time, we are right on time. So just thank you so much Dr. Perlman. Thank you to all of you for what was a very rich discussion today. We will take the comments, which I think were extremely helpful. We, I think heard loud and clear that we need to use a data-driven approach to get to the simplest possible scheme that we can for vaccination. And it should be as simple as possible, but not oversimplified a little bit like they say about Mozart's music. We will get there.

Just want to also just acknowledge, someone pointed out this a very opportune day to be having this this particular 178th Advisory Committee Meeting, it happens to be the 200th anniversary of the death of Edward Jenner. For those who don't know, was the person who helped initiate a vaccination for smallpox ultimately leading to the eradication of an infectious disease from the face of this earth.

With that, I just want to say that we will continue to do our work to protect and promote public health. We will continue to carefully monitor the safety of these vaccines and assess their effectiveness. And we'll also look forward to working with scientists inside of government, outside of government, in academics, in an industry towards a next generation of Covid vaccines that will hopefully have what some of the committee members have said, the greater depth and breadth and duration of protection that we'd like to see.

And so we really we've heard that message. And with that, in order to close on time, just another great round of thanks to the committee members and to Dr. Perlman. Thank you so much. Thank you to the audience who's tuned in today.

Adjournment

Dr. Paydar: Thank you, Dr. Marks, for closing comments. I wanted to thank the committee CBER staff for working so hard to make this meeting a successful meeting. I now call this meeting officially adjourned at 5:30 PM Eastern Time. Thank you.