Food and Drug Administration (FDA)

Center for Biologics Evaluation and Research (CBER)

182nd Meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC)

Zoom Video Conference

June 15, 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.

Transcript Produced By: Translation Excellence

3300 South Parker Road, Aurora, CO 80014

https://translationexcellence.com/

Acting Chair

Arnold Monto, M.D.	Professor, University of Michigan	Ann Arbor, MI

Voting Members

Adam C. Berger, Ph.D.	Director, Clinical and Healthcare Research Policy, NIH	Bethesda, MD
Henry (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, Vice President for Medical Affairs, Rosalind Franklin University of Medicine and Science	North Chicago, IL
Capt. Amanda Cohn, M.D.	Chief Medical Officer, National Center for Immunizations and Respiratory Diseases, CDC	Atlanta, GA
Capt. David Kim, M.D.	Director, Division of Vaccines, Office of Infectious Diseases and HIV/AIDS Policy, USDHHS	Washington, DC
Paul Offit, M.D.	Professor, Children's Hospital of Philadelphia	Philadelphia, PA
Steven Pergam, M.D.	Professor, Fred Hutchinson Cancer Center	Seattle, WA
Stanley Perlman, M.D., Ph.D.	Distinguished Chair, Departments of Microbiology and Immunology, and Pediatrics, University of Iowa	Iowa City, IA
Eric J. Rubin, M.D., Ph.D.	Editor-in-Chief, New England Journal of Medicine, Professor, Harvard T.H. Chan School of Public Health	Boston, MA

Industry Representative

Paula Annunziato, M.D.	Senior Vice President ID and Vaccines Global Clinical Development, Merck	North Wales, PA

Acting Consumer Representative

Randy Hawkins, M.D.	Physician, Pulmonary and Internal Medicine, Charles Drew University and Private Practice	Inglewood, CA

Temporary Voting Members

Bruce Gellin, M.D., M.PH.	Chief, Global Public Health Strategy, The Rockefeller Foundation	Washington, DC
James Hildreth, Sr., Ph.D., M.D.	President and Chief Executive Officer, Professor, Meharry Medical College	Nashville, TN
Jeannette Yen Lee, Ph.D.	Professor of Biostatistics, University of Arkansas for Medical Sciences	Little Rock, AR
Ofer Levy, M.D., Ph.D.	Professor, Harvard Medical School, Director, Precision Vaccines Program, Boston Children's Hospital	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	Hanover, NH

Michael Nelson, M.D., Ph.D.	Professor of Medicine and Chief of Asthma, Allergy, and Immunology Division, UVA Health & UVA School of Medicine	Charlottesville, VA
Arthur Reingold, M.D	Division Head, Epidemiology, University of California, Berkeley	Berkeley, CA
Mark Sawyer, M.D., FAAP	Professor, Vice Chair for Education, University of California San Diego School of Medicine	La Jolla, CA
Melinda Wharton, M.D., M.PH.	Associate Director, Vaccine Policy, National Center for Immunization and Respiratory Diseases, CDC	Atlanta, GA

Speakers and Guest Speakers

Rituparna Das, M.D., Ph.D.	VP, Clinical Development – Therapeutic Area Head, Respiratory Vaccines, Moderna	Philadelphia, PA
Filip Dubovsky, M.D.	Executive Vice President and Chief Medical Officer, Novavax	Gaithersburg, MD
Darin Edwards, Ph.D.	Executive Director, COVID-19 Lead, Moderna	Weston, MA
Ruth Link-Gelles, Ph.D., M.PH.	LCDR, USPHS, COVID-19 Vaccine Effectiveness Program Lead, NCIRD, CDC	Atlanta, GA
Kanta Subbarao, M.D., MPH	Director, WHO Collaborating Center for Research and Reference on Influenza	Melbourne, Australia
Kena A. Swanson, Ph.D.	Vice President, Viral Vaccines, Vaccine Research and Development, Pfizer Inc.	Pearl River, NY
Natalie Thornburg, Ph.D.	Acting Chief, Laboratory Branch, Coronavirus and Other Respiratory Viruses Division, NCIRD, CDC	Atlanta, GA

FDA Participants

Peter Marks, M.D., Ph.D.	Director, Center for Biologics Evaluation and Research (CBER), FDA	Silver Spring, MD
David C. Kaslow, M.D.	Director, Office of Vaccines Research and Review (OVRR), CBER, FDA	Silver Spring, MD
Jerry Weir, Ph.D.	Director, Division of Viral Products, OVRR, CBER, FDA	Silver Spring, MD
Sudhakar Agnihothram, B.Pharm., Ph.D.	Acting Senior Advisor to the Office Director, OVRR, CBER	Silver Spring, MD

Designated Federal Officer

Sussan Paydar, Ph.D.	Division of Scientific Advisors & Consultants (DSAC), CBER, FDA	Silver Spring, MD

DSAC Director

Prabhakara Atreya, Ph.D.	Division of Scientific Advisors & Consultants (DSAC), CBER, FDA	Silver Spring, MD

Committee Management Officer

Joanne Lipkind, M.S.	Division of Scientific Advisors & Consultants (DSAC), CBER, FDA	Silver Spring, MD

Committee Management Specialist

Lisa Johnson	Division of Scientific Advisors & Consultants (DSAC), CBER, FDA	Silver Spring, MD

Open Public Hearing Speakers

Melissa Miller		
Kermit Kubitz		
Mary Elizabeth Christian, M.D., BCBA, FACS		
David Wiseman, Ph.D.		
Don Ford		
Kevin McKernan		
Joaquín Beltrán		
Thair Phillips	Seniors Speak Out	
Amy Harth, Ph.D.		
Katherine Matthias, DO	Protect Their Future	
Karyne Jones	National Caucus and Center on Black Aging (NCBA)	
Burton Eller	The Grange	
Robin Strongin	National Consumers League	
Elle Pierce		

Contents

Call to Order and Welcome

Dr. Monto: This is Arnold Monto from the University of Michigan. I'd like to welcome the members, the guests, and especially the public to this, the 182nd meeting of the Vaccines and Related Biological Products Advisory Committee. Today we meet in open session to discuss and make recommendations on the selection of the strain or strains to be included in the periodic updated COVID-19 vaccine for the 2023-2024 vaccination campaign. I'd like to turn the chair over to Dr. Sussan Paydar, the Designated Federal Officer, who's going to give the administrative announcements, do the roll call, introduce the committee, and read the conflict-of-interest statements. Dr. Paydar.

Administrative Announcements

Dr. Paydar: Thank you, Dr. Monto. Good morning, everyone. This is Sussan Paydar, and it is my great honor to serve as the Designated Federal Officer for today's 182nd Vaccines and Related Biological Products Advisory Committee meeting. On behalf of the FDA, 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 and make recommendations on the selection of strains to be included in the periodic updated COVID-19 vaccines for the 2023-2024 vaccination campaign. Today's meeting and the topic were announced in the Federal Register Notice that was published on May 4th, 2023.

At this time, I would like to acknowledge outstanding leadership of Dr. Peter Marks, Director of Center for Biologics Evaluation and Research, Dr. David Kaslow, Director of Office of Vaccines Research and Review, Dr. Jerry Weir, Director of Division of Viral Products, OVRR, and Dr. Sudhakar Agnihothram, Acting Senior Advisor to the Office Director of Office of Vaccines Research and Review. I also would like to thank my Division Director, Dr. Prabha

Atreya, for her excellent leadership and my team, Ms. Joanne Lipkind and Ms. Lisa Johnson, whose contributions have been critical for preparing today's meeting.

Dr. Atreya: Excuse me, Sussan. No slides are showing.

Dr. Paydar: Devonte, would you be kind to show the leadership slide first? Great. And then this is the leadership slide that I was just talking about, and then the following slide is my own DSAC team. Great. That's Dr. Atreya with the team. I would also like to express our sincere appreciation to our AV team, Dr. Devonte Stephenson, Mr. Christopher Swett, and 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 at fdaoma@fda.hhs.gov. The transcriptionists for today's meeting are Catherine Diaz and Deborah Dellacroce from Translation Excellence.

We'll begin today's meeting by taking a formal roll call for the committee members and temporary voting members. When it is your turn, please turn on your 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. Arnold Monto. Dr. Monto, can we start please?

Roll Call and Committee Introductions

Dr. Monto: Thank you, Sussan. I'm Arnold Monto. I am at the University of Michigan School of Public Health, where I am an infectious disease epidemiologist. And I've worked on vaccines and occurrence of especially respiratory infection and their prevention.

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

Dr. Annunziato: Good morning. It doesn't look like my video has started. Well, good morning. My name is Paula Annunziato. I lead the Infectious Diseases and Vaccines Area at Merck, and I'm here today as the non-voting industry representative.

Dr. Paydar: Great. Thank you, Dr. Annunziato. Next is Dr. Adam Berger.

Dr. Berger: There we go. Good morning. My name is Adam Berger. I'm the Director of the Division of Clinical and Healthcare Research Policy at the National Institutes of Health. I'm a geneticist by training with additional training in immunology. Thanks very much.

Dr. Paydar: Great, thank you. Next is Dr. Hank Bernstein. Dr Bernstein.

Dr. Bernstein: Good morning. Good morning, everyone. My name's Hank Bernstein. I'm a professor of pediatrics at the Zucker School of Medicine, Hofstra Northwell. My areas of expertise are pediatrics and vaccines. Thank you.

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

Dr. Chatterjee: Good morning, everyone. My name is Archana Chatterjee. I have the honor and privilege of serving as the Dean of Chicago Medical School and Vice President from Medical Affairs at Rosalind Franklin University in North Chicago. I'm a pediatric infectious diseases specialist by background and training with expertise in the area of vaccines. Thank you.

Dr. Paydar: Great, thank you. Next is Captain Amanda Cohn. Dr. Cohn.

Dr. Cohn: Good morning, everyone. I am a pediatrician and a medical epidemiologist at the Centers for Disease Control and Prevention with expertise in vaccines and vaccine preventable diseases.

Dr. Paydar: Thank you. Next is Captain David Kim. Dr. Kim.

Dr. Kim: Good morning. David Kim with the National Vaccine Program representing the Office of the Assistant Secretary for Health at HHS. And my interest is in immunization and vaccine policy.

Dr. Paydar: Great. Thank you so much. Next is Dr. Paul Offit. Dr. Offit.

Dr. Offit: Yeah. Good morning. My name is Paul Offit. I am an attending physician in the Division of Infectious Disease at the Children's Hospital of Philadelphia, a professor of pediatrics at the University of Pennsylvania School of Medicine, and my area of interest is vaccines, specifically mucosal vaccines. Thank you.

Dr. Paydar: Thank you, Dr. Offit. Next is Dr. Steven Pergam.

Dr. Pergam: Thanks Dr. Paydar. I'm Steve Pergam. I'm a professor at Fred Hutchinson Cancer Center, an adult infectious disease position, with an interest in infectious diseases in immunocompromised hosts.

Dr. Paydar: Great. Thank you, Dr. Pergam. Next is Dr. Stanley Perlman. Dr. Perlman.

Dr. Perlman: Good morning. I am a professor of microbiology and immunology and a pediatrics at the University of Iowa. My specialty is pediatric infectious disease, and I've studied coronaviruses for many years.

Dr. Paydar: Great. Thank you, Dr. Perlman. Next is Dr. Eric Rubin. Dr. Rubin.

Dr. Rubin: Good morning. I'm at the Harvard T.H. Chan School of Public Health, the Harvard Medical School, Brigham and Women's Hospital, and the New England Journal of Medicine. And I'm an infectious disease doctor who studies tuberculosis.

Dr. Paydar: Thank you, Dr. Ruben. Next, we will do a roll call of our temporary voting members. I'll begin with Dr. Bruce Gellin. Dr. Gellin.

Dr. Gellin: Good morning. I'm Bruce Gellin. I'm Chief of Global Public Health Strategy at the Rockefeller Foundation with expertise in internal medicine, infectious diseases, epidemiology, and vaccine policy. Thanks.

Dr. Paydar: Great, thank you. Next is Dr. Randy Hawkins, our alternate consumer representative. Dr. Hawkins.

Dr. Hawkins: Good morning, Randy Hawkins. I'm internist and pulmonary physician in private practice, Charles Drew University of Medicine and Science.

Dr. Paydar: Thank you so much. Next is Dr. James Hildreth. Dr. Hildreth.

Dr. Hildreth: Good morning. I'm James Hildreth, the president and CEO of Meharry Medical College. I'm also a professor of internal medicine. I'm an immunologist by training, and I'm interested in viral pathogenesis. Thank you.

Dr. Paydar: Thank you so much, Dr. Jeanette Lee.

Dr. Lee: Yes, my name is Jeanette Lee. I'm a professor of biostatistics and a member of Winthrop P. Rockefeller Cancer Institute at the University of Arkansas for Medical Sciences. Thank you.

Dr. Paydar: Thank you so much, Dr. Lee. Next is Dr. Ofer Levy.

Dr. Levy: Good morning. My name is Ofer Levy, I'm a physician, internist, and Pediatric Infectious Disease Specialist at Boston Children's Hospital, where I direct the Precision Vaccines Program and Academic Program applying precision medicine principles for discovery and development of vaccines. A pleasure to be here this morning. Thank you.

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

Dr. McInnes: Good morning. Pamela McInnes, the retired Deputy Director of the National Center for Advancing Translational Sciences at the NIH.

Dr. Paydar: Thank you, Dr. McInnes. Next is Dr. Cody Meissner. Dr. Meissner.

Dr. Meissner: Good morning, Dr. Paydar. My name is Cody Meissner. I'm Professor of Pediatrics and Medicine at the Geisel School of Medicine at Dartmouth, and I am a vaccine subject matter expert at BARDA in the Department of Health and Human Services. I appreciate the opportunity to participate today. Over.

Dr. Paydar: Great. Thank you so much. Next is Dr. Michael Nelson.

Dr. Nelson: Morning. Thank you. I'm Mike Nelson. I'm a trained allergist immunologist. I'm chief of the Asthma Allergy Immunology Division in the Department of Medicine at the University of Virginia. I'm also president of the American Board of Allergy and Immunology. My interest is in vaccine immune responses and rare adverse events. Thank you so much.

Dr. Paydar: Thank you, Dr. Nelson. Next is Dr. Art Reingold.

Dr. Reingold: Good morning, everyone. Art Reingold. I'm an infectious disease epidemiologist at the School of Public Health at the University of California Berkeley.

Dr. Paydar: Thank you, Dr. Reingold. Next is Dr. Mark Sawyer.

Dr. Sawyer: I'm Mark Sawyer. I'm a pediatric infectious disease specialist at UC San Diego and Rady Children's Hospital of San Diego. My expertise is in the area of vaccines and vaccine policy.

Dr. Paydar: Thank you so much. Next and last but not least, Dr. Melinda Wharton.

Dr. Wharton: Good morning. I'm an adult infectious disease physician and I've been at the Centers for Disease Control and Prevention in the immunization program for many years, where I work in vaccine program and policy. And I trained as an adult infectious disease physician.

Conflict-of-Interest Statement

Dr. Paydar: Thank you so much, Dr. Wharton. Thanks everyone. We have total of 22 participants, 21 voting, and one non-voting member. Now I proceed with reading the FDA conflict of interest disclosure statement for the public record.

The Food and Drug Administration, FDA, is convening virtually today, June 15th, 2023, the 1 82nd meeting of the Vaccines and Related Biological Products Advisory Committee, VRBPAC, under the authority of the Federal Advisory Committee Act, FACA, of 1972. Dr. Arnold Monto is serving as the chair for today's meeting. Today, on June 15th, 2023, the committee will meet in open session to discuss and make recommendations on the selection of strains to be included in the periodic updated COVID-19 vaccines for the 2023-2024 vaccination campaign. 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 or appointed special government employees, SGEs, or regular government employees, RGEs, from other agencies, and are subject to federal conflict of interest laws and regulations. The following information on the status on 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 SGE consultants of this committee have been screened for potential 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 18 US Code 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts and grants, cooperative research and development agreements, teaching, speaking, writing patents and royalties, and primary employment. These may include

interests that are current or under negotiation. FDA has determined that all members of this advisory committee, both regular and temporary members, are in compliance with 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 outweighs the potential for a conflict of interest created by the financial interest involved or when the interest of a regular government employee is not so substantial as to be deemed likely to affect the integrity of 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 consultant 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 an 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 as special government employees and are screened and cleared prior to their participation in the meeting. They are voting members of the committee.

We have several federal and non-federal speakers, as well as some guest speakers today making various presentations on timely and relevant topics. The following speakers and guest speakers for this meeting have been screened for their conflicts of interest and cleared to participate as speakers for today's meeting. 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, Executive Director, COVID-19 Program Lead, Moderna Incorporated, Cambridge, Massachusetts; 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; Dr. Kanta Subbarao, Director, WHO Collaborating Center for Research and Reference on Influenza, The Peter Doherty Institute for Infection and Immunity, Professor, Department of Microbiology and Immunology, The University of Melbourne, Victoria Australia; Dr. Kena Swanson, Vice President, Viral Vaccines, Vaccine Research and Development, Pfizer Incorporated, New York, New York; Dr. Natalie Thornburg, Acting Chief, Laboratory Branch, Coronavirus and Other Respiratory Viruses Division, National Center for Immunizations and Respiratory Diseases, Center for Disease Control and Prevention, CDC, Atlanta, Georgia. 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 conflict-of-interest statement for the public record. At this time, I would like to hand over the meeting to our chair, Dr. Monto. Thank you. Dr. Monto.

Dr. Paydar: Thank you, Dr. Paydar. Next, it's my pleasure to introduce the FDA speakers. First, we are going to hear from the Director of the Center, Dr. Peter Marks, who will give us introductory remarks. He will be followed by Dr. David Kaslow, Director of the Office of Vaccine Research and Review. And Dr. Kaslow will talk about the considerations for selection of the composition of COVID-19 vaccines for the 2023-2024 season. Dr. Marks.

Opening Remarks — Dr. Peter Marks

Dr. Marks: Thanks very much, Dr. Monto. So my remarks will be brief. I want to thank the members of the advisory committee, today's speakers, the FDA staff, and those of you from the public joining today's 182nd meeting of the Vaccines and Related Biologics Products Advisory Committee. Though we're now at a period during which the number of new COVID-19 cases has declined notably, we still have SARS Coronavirus 2, the cause of COVID-19, as something that could be a real concern in the future, particularly as we move into the 2023-2024 winter season when we're concerned that we may have another wave of COVID-19 during a time when the virus has further evolved, immunity of the population has waned further, and we move indoors for wintertime. For this reason, we're gathered today and look forward to a robust discussion of the optimal composition for the 2023-2024 COVID-19 vaccines. We look forward to this

discussion. And to conclude, I just want to thank everyone for their contributions today to this very important topic. Thank you.

Considerations for Selection of the composition of COVID-19 Vaccines for the 2023-2024 Season — Dr. David Kaslow

Dr. Kaslow: Good morning. I'm from the Office of Vaccines Research and Review. Let me add my welcome to the 182nd meeting of VRBPAC and my thanks to the committee, the presenters, and the Center and Office staff for their preparation for this meeting. This is really a follow up meeting of the 26th January 2023 VRBPAC, where three topics were reviewed and discussed: harmonization of the strain composition across all ages and doses, simplification of the immunization schedule, and an approach to periodic updates of authorized and approved COVID-19 vaccines. Before reviewing today's meeting's objectives, which is focused on the third topic, strain selection for the anticipated 2023-2024 COVID-19 vaccination campaign, I'd like to start by providing a brief update on what's happened since the 26th January VRBPAC meeting. Next slide, please.

Thank you. A few noteworthy actions were taken, both in April. First was the consolidation of Emergency Use Authorizations to harmonize the strain composition from monovalent original strain to bivalent original plus Omicron BA.4/5 for all ages and all doses of mRNA vaccines authorized in the United States, and also in that EUA consolidation and an initial simplification of the immunization schedule, which I will review briefly. And secondly, a workshop on recombinant protein-based COVID-19 vaccines. Next slide please.

With the consolidation of EUAs in April, an initial step was taken towards a simplified age and risk-based immunization schedule for future periodic vaccination campaigns, or a single dose of a periodic updated COVID-19 vaccine would be approved for most of the US population,

including most adults, adolescents and older children, and young children previously vaccinated with the COVID-19 vaccine. And one or more additional doses would be approved for older adults and persons with compromised immunity as well as young children not previously vaccinated with a COVID-19 vaccine. Next slide, please.

In follow up to the discussion at the 26th January VRBPAC on the importance of recombinant protein-based alternatives to mRNA COVID-19 vaccines, FDA and BARDA co-hosted a joint workshop focused on recombinant protein-based vaccines to discuss the timely availability of additional updated COVID-19 vaccines beyond the current nucleic acid vaccines for periodic vaccination campaigns. The workshop reviewed the current epidemiology and five vaccine platforms, from bacteria to filament fungi and yeast to insect and mammalian cells, followed by a round table discussion on achieving timelines to launch these vaccines simultaneous with mRNA-based vaccines. Next slide.

So onto today's meeting, the objective of which is to discuss and make recommendations on the selection of a strain or strains to be included in periodic updated COVID-19 vaccines for the 2023-2024 vaccination campaign. FDA requests that VRBPAC consider and focus on three topics today. First, the need for a periodic update. Second, a change from the current bivalent to a monovalent composition. And third, selection of strain or strains if there's a need for a periodic update. Next slide please. Thank you.

To ensure we start today's review and discussion on the same page, I will briefly review the approach to periodic updates of current COVID-19 vaccines that was proposed at the 26th January VRBPAC meeting. As you'll hear again in several presentations today, the virus continues to evolve rapidly and immunity wanes such that restoration of a protective immunity will require vaccination with a periodically updated COVID-19 vaccine. In response, FDA

envisions an evidence-driven approach to monitor and update as needed the composition used in all COVID-19 vaccines with the goal to induce or restore protective immunity through periodic vaccination campaigns. Next slide, please.

As reviewed in January. This slide attempts to capture at a very high level the proposed continuous and iterative three-step process, in which integrated epidemiologic, clinical, and viral surveillance, viral characterization at the gene, phenotype, and antigen level, and vaccine effectiveness are integrated and 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, in a second step, submit to FDA a timely data package of their periodic updated vaccines for regulatory review. In the third step, real world evidence of the effectiveness of newly updated vaccines is collected and analyzed, which also starts the next three-step process. In essence, the review and discussion of the integrated data in step one and the vaccine candidate data generated at risk by manufacturers in step two are the core of today's agenda, which is shown in the next couple of slides. Next slide, please.

So we'll start the morning session with two presentations, both from our colleagues at CDC. The first presentation provides an update on bivalent vaccine effectiveness. The second CDC presentation, an update on the current epidemiology and circulating variants. We'll end that session with a presentation by the Chair of the World Health Organization's Technical Advisory Group on COVID-19 Vaccine Composition to review the TAG-CO-VAC May 2023 recommendation on the antigen composition of COVID-19 vaccines. After a short break, we'll next hear from the three currently authorized vaccine manufacturers, starting with Moderna. Next slide, please. Thank you. Then Pfizer and Novavax on their 2023-2024 vaccine candidates.

After a 30-minute lunch break, VRBPAC will reconvene for the Open Public Hearing session, which will be followed by FDA's presentation on considerations and recommendation for changes to COVID-19 vaccine strain composition. The FDA presentation will be followed by an additional 20-minute question and answer session for CDC, FDA, and sponsor presentations. After a short break, the committee will reconvene in open session to discuss whether there's a need to make a strain change for the 2023-2024 formula of COVID-19 vaccines; if so, whether there should also be a change from a bivalent to a monovalent vaccine composition; and if so, should the monovalent candidate be an XBB lineage-derived vaccine candidate?

After that discussion, the committee will be asked to vote on the following question. Next slide. Slide please. For the 2023-2024 formula of COVID-19 vaccines in the United States, does the committee recommend a periodic update of the current vaccine composition to a monovalent XBB lineage? Please vote yes, no, or abstain. After voting on the question, we then ask the committee to discuss the following topic. Next slide, please. Based on the evidence and other considerations presented, please discuss selection of a specific XBB lineage, for example, XBB.1.5, XBB.1.16 or XBB.2.3, for inclusion in the 2023-2024 formula of COVID-19 vaccines in the United States. After that discussion, the meeting is due to adjourn. And with that, I'll turn the floor back to you, our chair, Dr. Monto.

Q & A

Dr. Monto: Thank you, Dr. Marks and Dr. Kaslow. We have a few minutes for questions about what Dr. Kaslow presented in terms of the program for today's vote and then discussion. So questions for Dr. Marks and Dr. Kaslow, please raise your hands. I don't see any hands raised as yet.

Dr. Levy: I'm sorry, Dr. Monto, there are two hands raised by me and Dr. Gellin.

Dr. Monto: Okay. You go ahead.

Dr. Levy: And Dr. Bernstein. And now, Dr. Reingold.

Dr. Monto: Right.

Dr. Levy: Yeah. So thank you for the presentation. I found the brief description of the workshop by BARDA intriguing about the possibility of development of protein-based vaccines. And I'm wondering if more can be said about FDA's assessment of the landscape there and the anticipated trajectory of that approach towards coronavirus vaccines.

Dr. Kaslow: Thank you for that question. Maybe what I can do is just very briefly give a couple of key takeaways from that workshop. First, we heard from BARDA on Project NextGen and their strategy for that and the work that's involved in COVID-19 vaccine, which includes a centralized immunogenicity assay, harmonized clinical trial support, and support for early phase clinical trial manufacturing. Second and most obvious was a clear call from developers for early guidance on strain selection. While many of the recombinant protein-based technologies can work with a hundred-day window, it doesn't leave a lot of time for overcoming manufacturing technical problems that might arise, nor for generating preclinical and certainly clinical immunogenicity data to inform strain selection. Third, it’s clear that some work needs to occur at risk, and you'll hear about that today from all three manufacturers. But again, guidance on strains before the recommendation is made is made so that that at risk work can proceed.

And then finally, we heard about some of the platform strengths. And for some of these platforms, actually, new strain candidates can be manufactured quite quickly. Others can be rapidly scaled up, and others we heard about have and can provide more breadth or durability, and that's part of their vaccine platform. In short, what I can say is, is that recombinant protein-based platforms should be pursued, as should other platforms, as follow-on first-generation

vaccines. But as we'll hear and see in project Next Generation for the next generation of vaccines that may address things like durability, breadth, and potentially transmission.

Dr. Levy: Thank you. Thank you for that. It is going to be important to have additional shots on goal. Thank you.

Dr. Monto: Thank you. Next, Dr. Gellin.

Dr. Gellin: Yeah, David, thank you. And some of this may come up in the further discussions, but it'd be interesting to get some definitions on, well, what quote ‘campaign’ means and what ‘periodic’ means. But David, for you, it looks like step one is some, what triggers the review that would then lead to some consideration of an update? Thanks.

Dr. Kaslow: Thank you, Bruce, for that. And we will go into detail on some of those topics. What I think we envision is actually a continuous iterative process. So this is constantly looking at vaccine effectiveness, evaluating that, and looking at the viral evolution, and integrating that data to together to decide is there a need for a periodic update. So in essence, this is very similar, although it's different than what we do for influenza.

Dr. Monto: Thank you. Dr. Bernstein.

Dr. Bernstein: Yeah, I had a similar thought as Dr. Gellin. I really, you know, was thinking that hybrid immunity seems to be holding up quite well versus severe disease and death but less so as far as protection against infection. So I was trying to better understand when you use the words ‘2023-2024 campaign.’ Because I think that could create confusion in the public as far as how we're handling this or managing it. And I don't think it's exactly the same as what we do with influenza. So I think it's a bit in flux.

Dr. Kaslow: Agreed.

Dr. Monto: Thank you Dr. Reingold.

Dr. Reingold: Yeah. Hi. Thanks. So going along with the parallel to influenza, I'm just curious if you'll be able to say anything about attempts to coordinate with other countries and the international setting with regard to consistency of reformulation of Covid vaccines as we go forward.

Dr. Kaslow: Thank you for that question, Dr. Reingold. Absolutely. And I think that is one of the considerations that we're asking the committee to discuss as we talk about the strain selection. And so you will hear from the WHO TAG what their strain recommendation is. And you will also hear from Dr. Weir what the what the readouts are from various other global entities.

Dr. Monto: Thank you. Dr. Hildreth, last question.

Dr. Hildreth: Thank you, Dr. Monto. My question is for the Director. Both the WHO and the President have declared the public health emergency to be over. So, are these vaccines going to be given full approval or are they going to get EUAs, or do you still have the ability to use the UEA mechanism?

Dr. Marks: Yeah. Thank you, Dr. Hildreth, it's actually a great question. It turns out that the Public Health Emergency Declaration, which is a Section 319 declaration, which is over, is separate from the Declaration of the Secretary that allows us to make medical products available under Emergency Use Authorization, which is a Section 564 declaration. So we can still make products available under Emergency Use Authorization. It is our intent, though, for adults, as we move into this fall to the extent possible, to move as many of these over to licensed products through Biologics License Supplements. Whether we'll make it there for everything and for all age ranges, probably not for every age range, but certainly for adults, we are going to be looking

to try to work in that direction for as many products as we can. We do understand that having licensed products will help increase confidence.

And I just want to take this opportunity to say that, although I think we all certainly agree that COVID-19 is not influenza, from a public health vaccination campaign standpoint, in which you need to make tens upon tens of millions of vaccine doses, get them deployed, and get them into people's arms, and from the standpoint that people go inside in the United States during, at least in many states in the United States, during the months of November through March, it reduces to a similar type of campaign, barring some exceptional development of a resistant virus for us. So I think what we're seeing here is, I think we're, though it's not influenza for practical purposes, I think we have really a one chance this fall to get vaccines into arms, barring some, again, some need to update further, which we will do if need be. But that's, I think, what today's discussion is about. How to try to best come up with what goes into people's arms to offer the best protection during a period when, I think we do believe, we'll have waning immunity, at least in particularly in the older population, but probably throughout the population, as well as potential further evolution of the virus. Thanks.

Dr. Hildreth: Thank you, Dr. Marks.

CDC Presentations

Dr. Monto: Thank you. And thanks to Dr. Marks and Dr. Kaslow. Next, we're going to be hearing from the Centers for Disease Control. First, we're going to hear from Dr. Ruth Link-Gelles, who is the Program Lead at the National Center for Immunization and Respiratory Diseases at CDC. She will be talking about the, giving us an update on COVID-19 vaccine bivalent effectiveness. Dr. Link-Gelles, please.

Update on COVID-19 Vaccine Bivalent Effectiveness — Dr. Ruth Link-Gelles

Dr. Link-Gelles: Good morning and thank you for having me. Today I'll be presenting a summary of vaccine effectiveness data available from CDC studies, including vaccine effectiveness by variant period and among pregnant and immunocompromised people. Next slide.

Before diving into VE, I wanted to first highlight current COVID-19 vaccination coverage in the US, shown here by age group. Although most adults have received at least one dose — next slide — a minority of Americans have received a bivalent dose ranging from less than 8% in young adults to 43% in adults age 65 years and up. Next slide. Moving over to vaccine effectiveness, I will present updated estimates of bivalent VE by outcome and Omicron subvariant. I'll then provide an update on monovalent and bivalent VE in pregnant people and bivalent VE in adults with immunocompromising conditions. Next slide.

I'll start by presenting data on VE by outcome and Omicron subvariant in adults with data from CDC's VISION Network. Next slide. The VISION Network is a multi-state network based on electronic healthcare records. It uses a test negative design with cases having Covid-like illness and a positive PCR and controls having CLI with a negative PCR. Variant periods are designated for analysis based on the time when a novel sublineage became predominant, or more than 50% of the sequences in a study site's region. VE is adjusted here for age, sex, race and ethnicity, geographic region, and calendar time. Vaccination is determined via electronic healthcare record and state and city registries. Next slide.

This slide shows absolute VE of monovalent and bivalent vaccines against hospitalization on the top and critical illness on the bottom, and includes updated estimates from those recently published in CDC's MMWR. Critical illness here is defined as admission to the ICU or COVID-

19-associated death. Estimates for bivalent VE are shown by time since vaccination at 7 to 59 days, 60 to 119 days, and 120 to 179 days. Note here in the red box the median time since dose, which is nearly identical across the outcomes. Next slide.

As you can see, VE of the monovalent dose, shown here in orange with a median of over 13 months from vaccination, is relatively low. Initially, VE of the bivalent dose, shown in magenta, is high. However, waning is evident against hospitalization, on the top. Note the different pattern against the most critical illness, shown on the bottom. Although VE drops somewhat, it appears more durable, at 52%, a median of almost five months after the last dose. Next slide.

This slide shows the same information as the previous slide but now looking specifically at the period of Omicron BA.4/5 sublineage predominance. Note first that the categories are slightly different here at 7 to 89 days and 90 plus days, which was done due to the timing of the authorization of the bivalent vaccine and the end of BA.4/5 predominance. Next slide.

Here we see a similar pattern for the two endpoints with maybe a hint of less waning for critical illness, though confidence intervals are wide in overlap. Note that we do not split out BQ.1 and BQ 1.1 here, though previous VE estimates were similar across these sublineages. Next slide.

This slide, again, shows the same information as the previous slide, but now looking specifically at the period of Omicron XBB sublineage predominance. First, note the time since vaccination here, which is roughly one month longer for the bivalent booster groups due to the timing of XBB predominance. Here again, we see a pattern of waning against hospitalization with VE in the 7 to 89 days since a bivalent booster of 51% and VE in the 90 to 179 days of 20% and non-overlapping confidence intervals. The trend is different, however, for critical illness,

where we see a much smaller decline in the point estimate over time and overlapping confidence intervals. However, note that the confidence interval for 7 to 89 days is 64 points wide due to the timing of vaccine authorization and XBB predominance. Next slide. I'm sorry. One more.

I'll now move on to discuss bivalent VE against hospitalization from the IVY network. Next slide. The IVY network is a multi-state VE platform that uses a prospective case control design. For this analysis, participants were from 25 hospitals in 20 states with hospitalization between September 8th , 2022 and May 29th, 2023. Participants are adults hospitalized with Covid-like illness. Cases have a SARS-CoV-2 positive PCR or antigen test, and controls are negative for SARS-CoV-2 and influenza by real time PCR. Vaccination history is ascertained through, EMRs, state and local vaccine registries, and self-report. Next slide.

And here we have monovalent and bivalent VE against hospitalization in adults by time since last bivalent dose. VE of a monovalent dose, shown in orange, received a median of 393 days prior to vaccination, was 16%. IVY data show the same pattern as VISION data, with bivalent VE against hospitalization, shown in magenta, decreasing with time since vaccination, though note that the confidence interval for the 120 to 179 days is quite wide. IVY did not have power here to look at critical illness. Next slide.

Here, VE estimates are broken down into three sublineage predominant periods: BA.4/5 on the top, BQ.1 in the middle, and XBB on the bottom. First, note the time periods for analysis are different for each of the sublineage periods, shown here in the red boxes. For BA.4/5 VE is shown during the 7 to 59 days after the bivalent dose only. For BQ.1, VE is shown for 7 to 59 days and 60 to 119 days. And for XBB, VE is shown for 7 to 89 days and 90 to 179 days. These different time periods were due to the difference in timing of the sublineage predominance in relation to bivalent vaccine authorization. Next slide.

Next, note the differences in median time since last dose by variant period. Because of the relatively short period of predominance for BA.4/5 after authorization of bivalent vaccines, median time since last dose was only 25 days, with no ability to assess waning. Median time since last dose was longer for BQ.1 and XBB predominance. Next slide. Overall, note that VE looks similar during BA.4/5 and BQ.1, but appears to be lower during XBB predominance. Next slide.

Shifting gears a bit, I'll move on to present VE in special populations, starting with pregnant people. Next slide. I previously presented VE methods for the VISION Network, and here we'll share specific methods for the analysis among pregnant people. This analysis focuses on emergency department and urgent care encounters instead of hospitalizations due to sample size limitations and includes encounters among pregnant people aged 18 to 45 years. VE is adjusted for the same potential confounders is in the main analysis with the addition of underlying medical conditions, gestational age, Medicaid status, and site facility urbanicity. Finally, we'll present separate results from monovalent doses received prior to pregnancy and bivalent doses received during pregnancy, which was necessary due to the timing of bivalent dose authorization in the analysis. Next slide.

Here, we show results for the monovalent doses received prior to pregnancy, split by time before pregnancy, less than six months before pregnancy on the top and greater than or equal to six months before pregnancy on the bottom. Although confidence intervals overlap, we see a lower point estimate for doses received greater than or equal to six months before pregnancy, aligning with known patterns of waning in non-pregnant people. Next slide.

And here we show VE for bivalent doses received during pregnancy. Note that the CI is quite wide, but we see a point estimate of 61% for protection against emergency department and urgent care visits after receipt of a bivalent dose during pregnancy. Next slide.

CDC's Overcoming COVID-19 Network is another VE network which conducts active enrollment of SARS-CoV-2 positive cases and SARS-CoV-2 negative controls with a focus on children, including infants. This analysis looked at the effectiveness of maternal vaccination against COVID-19-associated hospitalization in in infants less than six months of age. Overcoming COVID operates in 25 pediatric hospitals in 19 states and included infants admitted between March 2022 and May 2023, so includes both monovalent and bivalent doses. Overcoming includes a parent interview for baseline demographics and clinical characteristics, and maternal vaccination status verified through state and local registries and medical records. Next slide.

This analysis differs from the VISION analysis shown previously. Instead of looking at monovalent vaccine received before pregnancy for outcomes of the pregnant person, this analysis looks at bivalent vaccine received during pregnancy for infant outcomes. Results here are looking at VE against infant hospitalization during the first zero to three months of life, on the top, and during the first zero to six months of life, on the bottom. The analysis did not have statistical power to look at VE separately for three to six months of age. Note that CIs are again wide, but the bivalent doses given to pregnant people helped provide protection against infant hospitalization during both the first three and six months of life. Next slide.

Finally I'll show updated in persons with immunocompromising conditions. Next slide. This slide shows updated data from those published in CDC's MMWR in May. VE is shown for hospitalization on the top and critical illness on the bottom. VE point estimates are generally

lower for those with immunocompromising conditions compared to the data showed earlier in the presentation for persons without immunocompromising conditions. Waning is not evident in this group, though this may be because of heterogeneity in immune response among those with immunocompromising conditions, or because of limited statistical power to detect differences over time. There were not enough cases to estimate VE specifically for different types of immunocompromising conditions, though VE has been shown in the past to vary based on type of condition. Next slide.

Moving on to summary and conclusions. Next slide. The results today have several limitations. First, for estimates of absolute vaccine effectiveness, if unvaccinated individuals are meaningfully different than vaccinated individuals, estimates may be biased. For interpretation of estimates of relative vaccine effectiveness, residual protection from prior doses is an important consideration and likely varies by severity of outcomes studied. Therefore, since absolute VE is somewhat easier to interpret and conclusions for relative and absolute VE for these analyses were the same, we've shared only absolute estimates today. We have limited information on prior infection in all platforms, although we know from seroprevalence studies that rates of prior infection in adults are high. VE estimates presented today are, therefore, a snapshot of how well the vaccine is working under current conditions. Lastly, VE against COVID-19-associated hospitalization from the platforms presented today represent individuals hospitalized with COVID-19 disease but may underestimate protection against critical illness. And thus, we've tried wherever possible to present estimates specifically for critical illness. Next slide.

In summary, current data from CDC VE platforms demonstrate that the bivalent booster doses helped provide protection against hospitalization and critical illness in adults, though we are seeing evidence of waning protection for hospitalization. For most adults, both in the

platform shown today and in the general population, more than a year has passed since they last received a monovalent COVID-19 vaccine. These individuals may have limited residual protection against hospitalization and should receive a bivalent booster dose. However, results from the VISION analysis show more sustained protection against the most critical COVID-19 disease. Data shown today appear to indicate that VE during XBB predominance may wane more quickly against hospitalization compared to earlier variant predominant periods, though this did not appear to be the case for critical illness. Vaccination during pregnancy helped provide protection against hospitalization for infants under six months of age, though with some indication that protection may be highest in the first three months, which aligns with understanding of timing of waning of maternal antibodies. CDC will continue ongoing monitoring of VE, including for all outcomes of interest and for all authorized vaccines in the US, with a focus on assessing new policy recommendations and VE in populations at higher risk of COVID-19. Next slide.

This concludes the presentation. I'd like to thank the numerous individuals and teams, both at CDC and at the study sites for their countless hours ensuring high quality data and analyses are available for VRBPAC. Thank you.

Q & A

Dr. Monto: Thank you Dr. Link-Gelles. This is an important presentation, and we have time for a few questions. Okay. Could somebody help me with the list somehow? My screen is not showing them at the moment.

Dr. Chatterjee: Dr. Levy is on, raising his hand.

Dr. Monto: Okay. Thank you. I still don't see the list.

Dr. Levy: Hi, Dr. Link-Gelles. First of all, thank you for an excellent presentation and highlighting distinct vulnerable populations in our country. I think the pandemic has taught us that one size does not fit all, and we have a diverse population in our country with subpopulations at different risk. You presented some data about immunocompromised adults. That's obviously a very large category, and it went by a little quickly. Can you say a little more about how that was defined and what different groups were included in there? I'm sure there's some heterogeneity, whether we're talking about solid organ stem cell transplant, leukemia on chemotherapy, primary immunodeficiencies. Obviously, there's a broad range, and there's probably nuance there between the different subgroups. I was wondering if you could just spend a little time telling us a little bit more about that category of individuals, because it's so important protect them, both for their own health and also to reduce emergence of other variants.

Dr. Link-Gelles: Thank you. Absolutely. So all of the categories that you mentioned are included in our definition, as well as a handful of others. I think your point is completely valid that it's a quite diverse population. It's also captured through ICD-10 codes here, which means that there's likely under-capture or mis-capture of some of these codes and conditions. So I think some of the estimates that we're seeing here today are really representing this diversity and heterogeneity amongst this group. We know from previous analyses of monovalent doses that those at highest risk in this category include people on current chemotherapy, those with solid organ or stem cell transplants. But because of just low case counts overall and unfortunately very low coverage in the general population with the bivalent doses, we weren't able to break out different categories and look at those specifically. I think what we've seen over time is that patterns of vaccine effectiveness for the bivalent vaccine have been very similar to what we knew from the monovalent vaccine. So I think it's probably appropriate to conclude that we

would see quite a bit of heterogeneity if we could break out VE by these different categories. And likely also that those most at risk continue to be sort of the most severely immunocompromised.

Dr. Levy: Thank you.

Dr. Monto: Thank you. Dr. Perlman.

Dr. Perlman: Yeah, so thank you for the presentation. And I just have a question, almost that's a more general question. So this seems like there's a contradiction between vaccine efficient efficacy of 20%, 40%, and the fact that ICUs and hospitals really have very few COVID-19 cases, especially the severe ones. So could you just define, explain why you think that's going on?

Dr. Link-Gelles: Right. It's an excellent point. And I think one of the reasons that, you know, many of our vaccine policy decisions are not based solely on vaccine effectiveness data, we also kind of need to understand the broader context, what we're seeing for hospitalization rates, and so on. I think what we're seeing here is a reflection of the hybrid immunity or high rates of prior infection that we have in the general population. So if you think of prior infection as representing, depending on age group, somewhere between 50 and close to 100 percent of people in the population, that means that the majority of the population has some underlying level of sort of baseline protection against COVID-19.

The bivalent vaccine, then, is giving them protection above and beyond what they have from their prior immunity due to prior monovalent vaccine or prior infection or both. And so I think what we're seeing here, even though this is absolute VE, so it's compared to people that are unvaccinated, is really can be thought of as a relative VE, sort of an incremental benefit of the bivalent vaccine on top of prior immunity from prior infection in this population. And so I think

our hospitals are probably staying less full because we do have such high levels of prior infection, prior monovalent vaccine, and then the bivalent boosters are giving those folks added protection on top of that hybrid immunity.

Dr. Perlman: Thank you.

Dr. Monto: Thank you. Dr. Gellin.

Dr. Gellin: Thanks. And thanks for the great presentation. I mean, throughout the day, we're going to have you know, crossover between Covid and influenza. We've already heard that. Dr. Marks mentioned about the increased risk late in the fall, in the winter. But given waning, I'd be interested — and, but I don't think we've established that this is seasonal. So given waning, if you were to advise someone, when's the optimal time to be vaccinated to have that optimal protection at a time when it's increased risk, when would that be?

Dr. Link-Gelles: It's an excellent question. I would have to look in my crystal ball, unfortunately. You know, I think there's a couple of considerations. One is that we know that, sort of, you're going to get the best incremental benefit if it's been longer since your last vaccine. But, of course, if you wait too long since your last vaccine, you're left with very little protection, and so you're at higher risk of severe illness. And so finding that sort of sweet spot where you're going to maximize your additional protection but also prevents sort of breakthrough infections due to waning or breakthrough severe disease due to waning, I think is the tricky part.

And then, as you say, we don't quite know sort of the pattern of SARS-CoV-2 to spread and whether it will turn out to be a seasonal virus this year or not. And I think we know from sort of past waves of Covid and vaccination that the very best time to get your dose is sort of right at the beginning of an uptick in disease. Of course, predicting that has been extremely difficult. I think this season will be telling to see if Covid sort of settles into a seasonal pattern or not. And

so I think right now what we know is that the vaccines do wane. They wane against hospitalization, maybe a little bit less so against critical illness, which is reassuring. But most Americans at this point haven't even received the bivalent and so are a year or more out from their monovalent dose and so have relatively little protection left.

Dr. Monto: Thank you. And last question in this group from Dr. Offit. Oh, Dr. Reingold has, as well. We'll go to you afterwards, Art. Dr Offit.

Dr. Offit: Yes. Thank you, Arnold. And thank you Dr. Link-Gelles. I just think one thing we don't seem to be talking about is the value of T-cells. I mean, we know that although clearly this virus evolves in terms of, involves away from recognition by antibodies at the receptor binding domain, the T-cell recognition, whether it's cytotoxic T-cells or T helper cells, has not really evolved. I mean, you still have 80 to 85% conservation. And T-cells are important in protection against severe disease. It's been shown redundantly, both in an experimental animals and in people. So I think the reason, and I guess in part an answer to Dr. Perlman's question, is the reason that we're not seeing this wave of serious illness as this virus evolves away from antibody recognition is because T-cells are important. So I do worry when we try and make this similar to the influenza model where it is a strain-specific phenomenon. I mean, if we miss with an influenza strain, as it's been true twice in the last 10 years, a miss is a mile. That's not true here because these T-cell recognition sites remain conserved. So I do think we do jump with the net here. And I do worry that in this kind of meeting when we talk about a seasonal flu vaccine that if the CDC then follows that up with a similar recommendation as we have for flu, which is everybody over six months needs a vaccine, I just don't think that's true. So I agree with your assessment that it is those highest risk groups that may benefit then from, from a booster dose,

but we need to define, continue to define who those high risk groups are and not make this a recommendation for everybody every season. Thanks.

Dr. Monto: Thank you. Dr. Reingold.

Dr. Reingold: Thanks, Arnold, again. Dr. Link-Gelles, thanks for your usual great presentation. So I probably missed this, but again, making the parallel to flu where we worry that old people like Arnold and me need a different vaccine, because you know, we don't respond as well, immunologically. Could you just summarize for me where you think, what we know about VE and waning in the older population, over 65, whatever, specifically compared to younger adults? Thanks.

Dr. Link-Gelles: Yeah, absolutely. I'm not sure if the backup slides are available, but if slide 28 could be shown, I've actually broken out here VE against hospitalization from the VISION Network amongst those 18 to 64 and 65 plus. Thank you. Yes. So these are updates from what was shared in the MMWR in May. And you can see here, I think, generally pretty similar patterns across older and younger groups. We've seen this phenomenon before with Covid, where sort of unexpectedly, VE appears to be higher or more sustained in elderly individuals, which is not the same pattern that we see in other diseases. I think this is likely due to some behavioral factors. We know from other studies that older adults have been more likely to continue masking, continue social distancing. So that's going to play into VE. We also know that older individuals have lower rates of prior infection, which means the vaccine sort of has more room to provide additional protection. And so I think we're picking that up here.

But for the most part here, we're not seeing sort of more severe waning in those 65 plus. I will say we are not powered, we don't have statistical power here to break out the most elderly age groups. And what we saw back in the era of monovalent vaccines, when we had higher rates

of both vaccination and hospitalization and could break out sort of 65 plus, 75 plus, and 85 plus, that it was really the 85 plus that had the quickest waning. Which I think makes sense from literature from other vaccines, as well. Again, we weren't able to do that here, but if you sort of take that data from the monovalent era combined with what we know about immunocompromising conditions and so on, it makes sense that sort of the oldest individuals are probably at the higher risk, but we just aren't powered here to pick that up.

Dr. Reingold: Thanks very much.

Dr. Monto: Thank you. And thank you to Dr. Link-Gelles for a very clear presentation. Now we're going to hear from Dr. Natalie Thornburg, Acting Chief of the Laboratory Branch in the Coronavirus and Other Respiratory Viruses Division at CDC, who will give us an update on current epidemiology of the COVID-19 pandemic and SARS-CoV-2 variants.

Update on Current Epidemiology of the COVID-19 Pandemic and SARS-CoV-2 Variants — Dr. Natalie Thornburg

Dr. Thornburg: Great, thank you. So in the first half of my presentation, I'm going to speak about SARS-CoV-2 variants and lineages, what's circulating currently, how they relate to each other genomically, and touch a little bit on how they relate to each other antigenically. And then in the second half of the presentation, I'll touch on the current epidemiology of COVID-19. Next slide, please. Next slide.

All right, so this is a graph of lineages, PANGO lineages, of viruses that have been circulating in the United States since January 2022. If you think back to prior to 2022, we had other variants circulating such as Alpha and Delta, which were getting Greek letter designations by WHO. This graph captures the very, very tail end of the Delta surge in the top upper left-hand corner in violet, with the PANGO lineage, B.1.617.2. So that is Delta. But since the beginning of

2022, end of 2021, when Omicron emerged, all lineages that have been circulating are Omicron. And so the virus has continued to evolve from Omicron into other Omicrons. If you look on the right side of the graph, which is 2023, everything that has been circulating are XBB viruses. So XBB viruses, as I've just said, are Omicron viruses, and they are descended from BA.2 viruses, which is a common progenitor of BA.4 and BA.5 viruses. They're named XBB viruses because they emerged from a recombination event from two different BA.2 viruses.

And so right now XBB.1.5, sort of dark medium blue, emerged in late 2022 and was predominant throughout the spring. And we have some new XBB lineages that are slowly increasing in proportion right now. Some XBB.1.9 viruses, as well as XBB.1.16 viruses. And just some patterns that I want you to notice here is that the virus has continued to evolve, continuously, really since the beginning of the pandemic. Some lineages do reach predominance. So if you look at sort of the aqua color there in the middle, that's BA.5, and that was a very dominant lineage that emerged, reached predominance, and then slowly contracted. But there are other lineages that do emerge that never reach predominance. So if you look at the yellow colors, BA.4, BA.4.6, did emerge, circulated at a significant proportion, but never really reached predominance. And then right now we have quite a bit of genomic variability, heterogeneity, with lots of different lineages, PANGO lineages circulating currently. Next slide please.

So that graph was showing the proportion of viruses. But if we scale the viruses to the number of positive nucleic acid amplification tests or case counts, we can see the relative number or estimated number of cases that each different lineage caused. So in that first Omicron wave, it was very, very large with great community burden, a very large community burden. And so if you look at the orange colors, B.1.1.150, BA.1.1, really the first Omicron viruses, they're estimated to have caused a very large number of cases. Each subsequent wave of viruses that

have been associated with a surge or a reach to predominance has caused fewer and fewer estimated cases because the case counts have been lower. And so you can see on the far right, we're looking at the number of cases, XBB.1.5 and currently circulating lineages are estimated to have caused, and we're looking at less than a million cases that each lineage has driven, really since spring of 2022, as opposed to that first Omicron wave when we reached the Y scale of about 5 million cases. Next slide please.

All right, so this is similar data, but just shown on a different x-axis. So this is weeks since variant proportion reached 1%. And so this graph you can see just how quickly individual lineages kind of took off after their emergence. So those first Omicron lineages really took off very quickly with exponential growth over just the first couple of weeks of emergence. More recent lineages, like XBB.1.5, have increased at a more steady, slow clip. Next slide, please.

All right. This is the current landscape of circulating lineages and viruses in the United States right now. And this is the national picture. So the left half of the graph is actual data. So those are weighted estimates of variant proportion based on genomic sequencing results. And then we utilize those results to model growth rates. And then the right side of the graph are model data that we call Nowcast. So these are bi-week bins. We update this data every other week with bi-weekly bins. And so the weighted estimates, the most recent weighted estimates that have been posted are for the week ending May 13th of this year. And the most recent modeled Nowcast data with estimated proportions are shown for the bi-week ending June 10th 2023, this year.

So XBB.1.5 is still predicted to be the most predominant lineage circulating in the United States, but it has been decreasing over the course of the past one to two months. Decreasing but at a slightly low proportion. The next most predicted predominant circulating lineages are

XBB.1.16, XB.1.9 , XBB.1.16.1. And the rest are listed beneath that. So you can see really all of the viruses that are circulating above 1% are XBB lineage viruses. Next slide please.

This is the picture of proportions of viruses regionally. This is the Nowcast data for the bi-week ending June 10th. So this is the model data by region. And you can see most regions are quite similar to each other, all regions, all of the viruses that are predicted to be circulating right now are XBB lineage viruses. XBB.1.5 is sitting just below half of circulating viruses in most regions, with a pretty heterogeneous picture of other XBB lineage viruses that are circulating in each regions. Next slide, please.

Okay, so what does that mean as far as how different are XBB viruses? And so, from the vaccine strain or from each other? So this is just a table demonstrating key substitutions in the spike receptor binding domain in different lineages of viruses. So across the top are some of the key residues where we see substitutions in different lineages of virus. And this is only the receptor binding domain of the spike protein, which is the part of the protein that binds to the cellular receptor and is often a major target for neutralizing antibodies. The reference sequence that's shown here is BA.4, BA.5. That is the vaccine formulation from the bivalent booster last year. So half of it was ancestral strain and half of it was this BA.4/5. As a reminder, BA.4 and BA.5, even though they evolved independently from a BA.2 progenitor, they have the same spike sequence. So in vaccines that only have spike, they can be used interchangeably.

The XBB viruses are kind of listed at the bottom of the table. And XBB viruses, we've observed convergent evolution, meaning we see the same spike sequence in multiple lineages of viruses, indicating some selective pressure. But that means multiple lineages of the virus have exactly the same spike sequence. So even though they are shown independently on our Covid data tracker, they have the same spike sequence and might look very similar or the same to

someone's immune system. And you can see that there are a few substitutions across the spike receptor binding domain, especially in comparison to the reference sequences. There are 9, 10 substitutions in the receptor binding domain. As a comparison of the Delta to Omicron shift, we saw about 15 substitutions across the receptor binding domain in that shift. Of course, that was a very dramatic shift because it happened so quickly. This has been accumulating more slowly over time with emergence of some BA.5 sublineages last fall, which accumulated a few mutations, and then these XBB viruses, which have accumulated a few more mutations. So it's been sort of a slower drift this year as opposed to that Delta to Omicron shift.

The bolded lineages are the lineages that are currently increasing in proportion. So you can see XBB.1.9, .1.9.2 are both increasing, but they have the same spike sequence, especially in comparison to XBB.1.5 and XBB.1.16 and its sublineage .1.16.1 also have the same spike sequence and have one substitution in comparison to XBB.1.5. And the other two that are increasing in proportion right now, .1.9.1 and .1.9.2. There's one additional lineage, XBB.2.3, that's increasing in proportion right now, and it also has one substitution in comparison to .1.5, but it's at a different location than .1.16. It has got a substitution at 521, whereas .1.16 has a substitution at 478. Next slide please.

All right. So this is a co-crystal structure of the spike hetero, or the spike trimer, in complex with ACE2. So ACE2 is the cellular receptor that the virus binds to when it's infecting cells. So as a reminder, spike is a trimer. It's got three protomers. It's got three sections that are exactly the same that bind to each other. Each protomer of spike has a receptor binding domain that's shown in green and red together. That's the area that binds to the cellular receptor, ACE2. The S1 has the most heterogeneous, the least conserved sequence of Spike. S1 is made up of the N terminal domain that's shown in blue, a sort of middle part that's shown in purple, and then the

receptor binding motif, which is in green and red together. And then the S2 region, that's the part that inserts into the viral membrane, and that's fairly conserved and doesn't generally accumulate a lot of substitutions.

So we have some highlighted substitutions. These are changes that are in spike in comparison to the 4/5 reference sequences. And we've specifically highlighted substitutions that are observed in the N-terminal domain as well as the receptor binding motif. Now, the N-terminal domain, while it doesn't bind to the cellular receptor, some weakly neutralizing antibodies can bind to that region of the protein, likely because of its proximity to the receptor binding domain. So there are some substitutions that are observed both in XBB.1.5 and XBB.1.16 in comparison to reference sequence. We've highlighted a couple of the two changes that are different between XBB.1.5 and XBB.1.16 in comparison to each other. And I'll zoom in on those on the next couple of slides. Next slide please.

All right, so you can see a closeup, and I'll go even closer in the next slide. You can see the closeup of two substitutions that are observed in XBB.1.16 relative to BA.5 that are not found in XBB.1.5. There's one that's in the receptor binding motif, the smaller section of the receptor binding domain that binds to ACE2. And it's kind of tucked in there on the right side of the receptor binding motif. And there's another one that's embedded inside the N-terminal domain, which is shown in blue on the left and circled in yellow, and that's at position 180 of the spike protein. Next slide please.

Okay, and this is just an even closer up for you to better see those two substitutions. So you can see how they could, in theory, affect any sort of activity of spike or neutralizing activity. Really that 180 substitution is kind of tucked deep into the receptor, or in the N-terminal domain,

where that change at 478 is more likely to play a role in either receptor binding or neutralization because of how close it is to the ACE2 binding site. Next slide, please.

Alright, so how does how does the accumulation of mutations affect neutralization of the virus? There have been a couple of studies that are published looking at neutralization of some of these XBB viruses. And I've pulled out two that are very, very recent that have data from both XBB.1.5 and XBB.1.16. So when the immune history of the population was similar, back when most folks were naive or vaccinated, unvaccinated, or just previously infected, it was pretty simple to interpret neutralization. That's become more complicated as our immune history has become more complicated, and we now have combinations of receiving different vaccines, different timing of vaccines, as well as infection with different lineages of viruses.

So this is one example of neutralization assays that were published in Lancet ID. This is using pseudovirus neutralization assays with sera from humans who were vaccinated and then infected with BA.2 virus. That's shown in the left panel, G. Vaccinated and then had BA.5 infection, that's shown in the middle panel. Or animal sera, specifically hamster sera, from hamsters that were infected with XBB viruses. So what you can see here, they've done neutralization assays with one of the original lineages of Omicron, B.1.1, a BA.2, BA.5, and then different iterations of XBB viruses. And you can see from persons who were infected with BA.2 or BA.5, you see reduced neutralization of BA.2 and then even more reduced neutralization of BA.5 in comparison to the original Omicron virus. And that is statistically significant. Those red stars indicate statistically different from the titers of B.1.1.

And then the XBB lineage viruses, you see a more dramatic decrease in neutralization titers in comparison to one of the original Omicron viruses, B.1.1. Notably, that difference is more dramatic in persons who were infected with BA.2 than BA.5 viruses. So there are still

some individuals who had been infected with BA.5 who retain some neutralization activity against the XBB viruses. When you look at the blue hash marks, that indicates statistical significance of whatever virus they're testing against XBB.1.5. And so there is a statistical difference with XBB.1.5 with neutralization against BA.5 and BA.2 in the BA.2 breakthrough infections, just against BA.2 and BA.5, and after BA.5 breakthrough infections against XBB.1.16 as well as BA.2 and BA.5. But the actual titers are listed in the parentheses kind of just above the XBB lineage. And you can see, while there is some statistical difference between XBB.1.16 and XBB.1.5, the absolute titers are pretty similar to each other, 162 and 252, versus the dramatically different from earlier Omicron lineage, that 6,000 and in the thousands against BA.2 and BA.5.

When you look at hamster sera, so a little bit easier to interpret because you know the immune history of those, infecting hamsters with XBB.1 virus and then using their sera for neutralization against other viruses. There is very similar neutralization against all of the XBB viruses, indicating that they're antigenically similar in these simpler immune histories. Next slide, please.

All right. So this is another study that was published in Cell and Molecular Immunology. They look at fewer viruses in this study. This is all using human sera for neutralization, using pseudo viruses. These are neutralization titers of XBB pseudo viruses. Looking at B.1, one of the original Omicron lineages, XBB.1.5, and .1.16. There are sera collected from persons who were vaccinated with breakthrough infection, that's what BTI means, breakthrough infection, persons who received four doses of monovalent booster vaccines, and persons who received four doses of vaccine that include a bivalent booster. The absolute titers, the geometric mean titers, are listed across the top of top of the graphs. And the reactivity, the number of reactivities, you can

see the number of donors that were in used in each group. So it's about 14 or 15 in each group. And then statistical significance is shown with the asterisks. So in all of the groups, the titers against the XBB viruses were lower than they were against the original Omicron, but they were not statistically different from each other. Next slide, please.

All right, so this is an antigenic cartographic map from David Ho's laboratory looking at how similar different Omicrons are to each other. And just a reminder of what an antigen cartographic mind is. It's a way to visually represent neutralization data that clusters similar virus groups together, just for easier interpretation of how similar viruses might be to each other. So, to do this, scientists do a matrix where you take different kinds of sera, sera from vaccinated persons, vaccinated animals, and different viruses, collect neutralization titers, and then just do some math to generate proportional distances according to whatever the titers were. And in this case and in this particular map, one AU, or arbitrary unit, equals a twofold change in neutralization.

And you can see they use different types of sera. They've used sera collected from persons with three shots of the original formulation of vaccine, those with some BA.2 breakthrough infections, persons with BA.4 or 5 breakthrough infections, persons who had four shots of the original formulation of vaccine as well as some sera collected from persons with three shots plus bivalent vaccines. And what I'd like you to see is that BA.4, BA.5, and BA.2 viruses cluster together. Some of the BA.5 evolved lineages, which are BQ.1 and BQ.1.1, cluster pretty close together up there in the top. And then these two XBB viruses that they've tested, XBB and XBB.1, also cluster together.

So this was one manuscript that they had published in Cell. This same set of authors have a preprint posted, as well, where they do a similar study, but they also include XBB.1.5 and

XBB.1.16 in their antigenic cartography analyses. And those two viruses, XBB.1.5 and .1.16, cluster very close to each other in that preprint study. Next slide please. Thank you.

Okay, so I'm going to pause here and change and talk a little bit about the epidemiology of COVID-19 right now. Next slide. So this is data that we gathered last week. As of June 3rd of this year, there have been 6.2 million reported hospitalizations and 1.1 million reported deaths associated with COVID-19. Next slide, please.

These are the weekly trends of SARS-CoV-2 test percent positivity in the United States. That was March 14th 2020 through last week, June 3rd. Because of different testing habits different data reporting requirements since the expiration of the public health emergency, percent positivity is our best indicator of community transmission at any currently. So on the far right of the graph, you can see , we're sitting at just below 5% test positivity. For, for the week ending June 3rd you can see that really, really big Omicron wave in the winter of 2021, early 2022, where test positivity went above 30%. There was that BA.5 wave that we observed late last summer into early fall where test positivity peaked at just below 15%. And then of course we saw another expected winter surge through the end of 2022 into the beginning of this year that correlated with a rise of XBB.1.5 predominance, and that peaked at just above 10% positivity. Since then, we've been decreasing in percent positivity and are still sitting at kind of right around 5%, which we have been for about a month. Next slide, please.

All right, so the x-axis is a little bit different here. This is just for one year, since June of 2022. These are patients diagnosed with COVID-19 as a percent of all emergency department visits by age groups in the United States. And so in this, we can capture the BA.5 wave, kind of there on the left, as well as the winter surge that was associated with XBB.1.5 coming into predominance December-January of this year. And you can see that hospital visits to er do

correlate with community transmission and that the older adults, 75 and older, continue to be the group with the highest rate of emergency department visits. Although across all age groups, you can see bumps in ER visits with each wave of community transmission. Next slide please.

Alright, so this is looking at hospital admissions since the beginning of the pandemic, hospital admissions per 100,000 population by age groups. So this is the same age groups I showed in the previous slide. So you can see, really since April of '22, which was after the first Omicron wave, even during the BA.5 wave, I've kind of highlighted since April 2022 in this blue box. The BA.5 wave you can see in the bump on the left in the blue box and the XBB.1.5 wave on the bump on the right. And you can see since April 2022, we've observed much lower hospital admissions among younger persons relative to older age groups. And so older age groups, 75 years and older, continue to have hospital admissions, sort of bump with each increase, each wave of community transmission. But lower age groups, including 74 and younger, we've seen a dramatic decrease in hospital admissions. Next slide please.

Alright, and so this is similar data, but COVID-19 associated deaths. And really similarly, since April '22, we have a much lower death rate among younger adults and younger persons relative to older age groups. But we do still have some COVID-19 associated mortality, especially with bumps with community transmission, especially in adults that are 75 years and older. Next slide, please.

All right. So I mentioned earlier that, you know, we've really seen a changing landscape in sort of the immune history of our population. And this is some seroprevalence data that was generated from blood donors that was just published in MMWR a couple of weeks ago. And so in this study, they've collected residual sera from blood donors and collected vaccine information from surveys and determined, using antibodies against the nucleocapsid protein, which should

only be generated after infection and spike protein, along with survey data to identify proportion or prevalence of persons with previous vaccination and infection, that's dark blue, previous infection without vaccination, that's sort of the medium blue, previous vaccination without infection is also a lighter medium blue, and then no previous infection or vaccination. And you can see a dramatic increase over the course of this year, April 2021 through sort of September 2022, a dramatic increase of persons who have hybrid immunity. And so that's been accumulating down from below 10% in April to June 2021 to almost half of the population who have both vaccination and infection more recently. Next slide please.

Alright. Okay. So what does this very complex landscape mean in terms of protection against mortality? And what can we glean from mortality of vaccinated persons and persons who haven't been vaccinated? So this is some data from an MMWR that was released today that is examining the mortality rate ratios in adults 65 or older, comparing unvaccinated adults to those who received bivalent booster by time since vaccination. A very similar analysis has been published recently, but this updated one encompasses XBB.1.5 timeframe, the frame since that's been predominant, as well as looking at durability. So this is divided by time since vaccination. The lighter blue, two weeks to two months, versus three to six months in the darker blue. And then during times of BA.5 predominance on the far left, BQ.1 and BQ.1.1, which is a BA.5 sublineage, in the middle, versus XBB.1.5 here on the right. And at two weeks to two months post-vaccination, the mortality rate ratio declined from 16.3 during that BA.5 period to 8.4 during XBB.1.5 predominance, which represents a reduction in the crude vaccine effectiveness of 94 to 88%. Similar mortality rate ratios were observed among people between the two weeks and two-month time period compared to the three-to-six-month post-vaccination period,

indicating good durability of vaccination, of bivalent booster vaccination, against mortality. Next slide please.

So of these persons who are still getting severe disease and mortality with COVID-19 infection, we have extensive data describing risk factors of persons who are still at risk for severe illness. And those include unvaccinated persons. They continue to be at higher risk for severe illness compared to vaccinated persons. Most, at least 75%, of vaccinated people who develop severe COVID-19 illness have multiple risk factors, including older age. Most are at least 65 years or greater, but the risk increases with age, incrementally, as well as underlying medical conditions, with risk increasing with the number of underlying medical conditions, including immunosuppression, diabetes, chronic kidney disease, lung disease, cardiovascular disease, and chronic neurological diseases. Fortunately, antiviral drugs can help reduce risk of severe illness in persons at higher risks, regardless of vaccination status.

Next slide I believe is my summary slide. So Omicron XBB lineage viruses have predominated since early 2023 and continue to predominate. XBB lineage viruses have reduced neutralization if you compare them to earlier Omicron lineages but have similar neutralization profiles to each other, indicating they're antigenically similar. Declining rates of severe illness since January 2023 have been observed, but older adults, especially those 75 years and older, experience greater relative burden of severe illness since April of 2022. And although there's some evidence of immune evasion observed for Omicron XBB.1.5, bivalent boosters provide robust protection against COVID-19-associated death without evidence of waning for at least six months post-vaccination.

And next slide. That is the conclusion of my presentation. I would like to thank all of the CDC contributors to this presentation. Thank you.

Q & A

Dr. Monto: Thank you, Dr. Thornburg. Avery comprehensive presentation which will help us a great deal in our discussion later. You didn't bring up one of the variants that we are to consider our, in our discussions, XBB.2.3. Do you have any information about where it would sit in the antigenic cartography? I think it's very important, the fact that what we're going to be considering, they all are much closer than what we've had to consider before.

Dr. Thornburg: Yes. Let me see, let me take a quick look at my slide number. So I didn't pull up any antigenic cartography data, but if you could pull up the slides again and go to slide eight, that shows the key changes in the spike receptor binding domain, XBB.2.3 is listed there. So if you could go to slide eight. that would help me. Thank you so much. Okay, so you can see XBB.2.3 is listed on the bottom there. And the bottom three are really the three lineages that you're looking at. So you can see XBB.2.3 has one substitution in comparison to XBB.1.5. And there's two substitution differences between 1.16 and 2.3. If you look at 478 and 521, you can see the differences there. So they're all quite similar to each other but have some minor changes in the receptor binding domain, which is probably the most important region for neutralization.

If you could go ahead two slides, we could kind of take a look at where it's sort of located on the crystal structure. Maybe go ahead. One more. Okay. So it's not highlighted here, but you can kind of see the numbers where it might be located. So you can see the closest residue that is listed there is 490. So it would be, you know, 30 away from that. So it would be near the interface of XBB, or of spike and ACE2. It would be near the interface. So, you know, a similar difference to XBB.1.16 to XBB.1.5.

Dr. Monto: But it's close?

Dr. Thornburg: Yes. They're all, they're, yeah. If you go back to that, if you want to go back to slide eight and everyone would like to study that, they're very close.

Dr. Monto; No, we, we don't need to do that.

Dr. Thornburg: Okay.

Dr. Monto: The point is these are all relatively close compared to what we've —

Dr. Thornburg: Very close.

Dr. Monto: — been dealing with in the past.

Dr. Thornburg: Yes.

Dr. Monto: Okay. Dr. Levy.

Dr. Levy: Thank you, Dr. Thornburg, for a very illuminating presentation. The British statistician George Box once said, "All models are wrong, but some are useful." You alluded to some of the models that you folks are looking at. Obviously, we want to gather this data and try to project what does the future hold. And my brief question to you, twofold. One is how do you validate these models? How much confidence do you have in your ability to project forward? Will the XBB.2 predominate, you know, in a few months? That's obviously an important question as we think about vaccine composition.

And then the second question is the XBB.2 variant, the list of amino acids that you listed there showed a switch of a serine instead of a proline. As you know, prolines are very important to introduce disruption in secondary structures of proteins. So does that S protein then have a very different structure? Because the x-ray crystallography modeling you showed us was off the one variant.

Dr. Thornburg: Yeah. Let's see. You asked me two questions. So one, predicting forward what lineages will emerge?

Dr. Levy: Yeah. And how robust those models are, whether you can validate them. How good is the validation of the models? Yeah. For projection.

Dr. Thornburg: Yeah. I mean, our Nowcast modeling is good into the present. We can't really look into the future as far as lineages are concerned. We can tell you the lineages that are increasing now and it is unlikely to go backwards. So lineages that have swept through predominance and are decreasing in proportion, we're not likely to go backwards. We haven't observed that yet —

Dr. Levy: The question is, is there any effort to apply artificial intelligence, machine learning to project forward this all the data we have?

Dr. Thornburg: No, we don't have that sort of modeling.

Dr. Levy: Got it. And then in terms of the XBB.2, the serine instead of the proline, does that imply it has a very different structure than the one?

Dr. Thornburg: I mean, I wouldn't, you know, spike is a really huge protein. And so the sort of stability of the up-down could be affected. And that could absolutely affect affinity to ACE2, but the full structure of the spike protein by that one substitution, it is a very large protein, and I doubt that we would see any really dramatic thank you difference in the full structure.

Dr. Levy: Thank you.

Dr. Monto: Thank you. Dr. Offit.

Dr. Offit: Yes, thank you. Thanks, Dr. Thornburg. I thought your observation that you had fairly prolonged protection against severe disease for at least six months after a boost suggests that you may not just be boosting antibody responses, but boosting memory cells, or at least the

frequency of memory cells, memory B or T cells. Do you know of any studies that have really looked at that? Because that would be important to know.

Dr. Thornburg: I think it's, so I don't have any of that data here. I do think we likely get a boost of anamnestic response when we get bivalent booster doses. And that does induce a germinal center reaction and further affinity maturation of antibodies and memory B cells. And that, we get that boost in antibodies, but that also gets us to higher quality antibodies. Now that function is dependent upon T-cell help, and the ability to generate that T-cell help is very different in different populations. So of course, in older adults who are experiencing immunosenescence, their ability to mount a really robust germinal center reaction is going to be abrogated in comparison to younger adults.

Dr. Offit: No, it’s important to know only because if you really do have a higher frequencies of memory, B and T helper, cytotoxic T-cell, you may not need to then boost the following year or the year after that. I mean, so that would be interesting to know.

Dr. Thornburg: Yes.

Dr. Monto: Thank you. Dr. Meissner for the last question.

Dr. Meissner: Okay. Thank you, Dr. Monto and Dr. Thornburg. What fascinating presentation. You're really taking this virus apart on a molecular level. The question I'd like to ask you since we're trying to anticipate a little bit where things might go, is the evolution of XBB. And XBB, I think, has been described as a recombination of two viruses, which is different than the other mutations, which are point mutations, additions, or deletions, or substitutions. And I don't think of linear RNA viruses as undergoing recombination. I think more segmented viruses as being able to do that. So does that surprise you? Isn't that an unusual event? What, do other linear single stranded RNA viruses do this?

Dr. Thornburg: It's pretty unique to Coronavirus. Coronaviruses are buggers. They have very, you know, they have very huge genomes, really at the upper limit of stability for RNA genomes. And as part of that, they have this very complex replication cycle that involves discontinuous transcription. And it's through that really complex generation of mRNAs during transcription and the translation replication process that probably it's got these motifs throughout the genome that are repeated and the same. And it's probably this complex replication cycle along with this repeated motif that allows recombination. So this is unusual to Coronaviruses specifically.

Dr. Meissner: So is there is a risk then that this could happen again with this coronavirus.

Dr. Thornburg: Absolutely. Recombination events happen periodically with coronaviruses. They generally have to happen with viruses that are cocirculating. So, you know, there were probably two BA.2 viruses that were co circulating. So I wouldn't imagine we would go XBB to ancestral, because there is no ancestral virus that is circulating. So it would have to be during cocirculation.

Dr. Monto: And that's what makes this prediction, pushing prediction models so difficult. Thank you so much Dr. Thornburg. We're now going to switch over to Dr. Kanta Subbarao, Director of the WHO Collaborating Center in Melbourne, and also associated with the Peter Doherty Institute for Infection and Immunity in Melbourne, who fortunately is in Canada, and who will report to us on the WHO TAG committee, the Technical Advisory Committee, recommendations on the composition of COVID-19 vaccines going forward. Dr. Subbarao, please.

WHO Presentation — WHO TAG-CO-VAC May 2023 recommendation on the antigen composition of COVID-19 vaccines — Dr. Kanta Subbarao

Dr. Subbarao: Thank you very much, Dr. Monto. I'm going to share my screen so I can control my slides from here. So hopefully that works for you. Can you just tell me if you can see my slides, Arnold?

Dr. Monto: We can see them. Looks good.

Dr. Subbarao: Perfect. All right, thank you. So I was asked to talk about the deliberations of the TAG-CO-VAC, which is the technical advisory group on COVID-19 vaccine composition. And this is from a meeting that we held in May. So the functions of the TAG-CO-VAC, and I know I've spoken to VRBPAC before, but the key element of what we are tasked to do is to recommend to the WHO, for each of the COVID-19 vaccine platforms, whether adaptations are needed, so that the vaccines continue to safely provide protection against variants as they emerge.

So before I go on to what's going on this year, I do want to set the stage a little bit with what was happening a year ago. So in June of 2022, I will remind you that we were in the midst of the early Omicron lineages. So Omicron BA.1 and BA.2 had emerged. Omicron BA.2 remained the predominant lineage globally, and BA.4 and 5 had started increasing in proportion. And at the time, we looked at the antigenic cartography data, which I came in at the tail end of Natalie Thornburg's presentation. So you know, I know she's explained how antigenic cartography works. And the original cluster of viruses is up here in the top left. The Delta variant is within fourfold of the original, and BA.1 and BA.2 were further out. And this is another aggregated antigenic map of the variants at the time. So what we had is a situation where Omicron lineage viruses had emerged, and they were antigenically quite distinct.

We had a lot of uncertainties back a year ago. We didn't know what the trajectory of SARS-CoV-2 evolution would be. We didn't know whether future variants would evolve from the previously circulating variants or where the evolution would continue from Omicron. We didn't know very much about the performance of monovalent Omicron vaccines. We didn't know whether an Omicron monovalent vaccine would offer a similar cross-reactive immunity and cross-protection from severe illness caused by other variants and unprimed individuals as the index-based vaccine had done so well. It wasn't clear to us at the time whether an Omicron containing bi- or multivalent product would elicit cross-reactive responses in humans that would be equivalent to those elicited with sequential vaccine approaches. And we assumed that the safety and reactogenic of the variant-specific vaccines would be similar to the currently licensed vaccine. So there was a lot of uncertainty, as a result of which we recommended that the effort be to try to improve the breadth of protection that certainly the existing ancestral vaccine produced, provided very good protection against severe illness and death. But if you wanted to extend that protection beyond to cover new variants, that we could recommend including BA.1 or an Omicron variant. And at the time, of course, we also recommended that the ancestral strain be kept in play because we had a lot of confidence about the protection it provided from severe illness and death, and we had a lot of uncertainty as to where the trajectory of revolution would go.

So if you fast forward to May of 2023, we're now looking at the current situation in May of 2023 cases on the left y-axis deaths on the right y-axis. The solid line is the deaths. The color-coded bars represent the different WHO regions. And these are COVID-19 cases and deaths reported to the WHO from January of 2022, May of 2023. And so as we heard before, these are some of the surges that have occurred.

Another thing that has really changed significantly over the past period of time is seroprevalence. And so these are series of seroprevalence studies conducted in different regions of the world going down on the left and going across over time. And at the very bottom, circled in green here, are the global data, which indicate that seroprevalence has increased all across all regions and is now sitting at about 90% in most regions. And so we really have a very different situation of population immunity than we did earlier in the pandemic. So what is the protective effectiveness of such hybrid immunity?

And these are data, the references down below here. We're looking at percent protection against hospital admission or severe disease versus any infection. And the x-axis is time since the last vaccination, or infection in months. So these lighter color, the red spectrum colors, are the primary series of vaccination and a booster dose. And you could see that they provide protection against severe illness and hospital admission that wanes gradually sometime after about six months. But the waning of protection against infection comes quite a bit faster. And now if you look at the blue spectra, these are people that have hybrid immunity, infection plus vaccination, and that's the blue lines here. And you can see that with hybrid immunity, protection against severe illness and hospitalization is boosted. It is also boosted against infection, but that continues to have a similar trajectory of decline in protection from infection. So protection. And these are data from the period when Omicron variants have been circulating.

And so the evidence that we reviewed at our committee in May covered a number of different topics. We reviewed the evolution of the virus, including the XBB.1 descendant lineages and their impact on cross neutralization and cross protection following vaccination or infection. We looked at vaccine effectiveness data of currently approved vaccines during a period of XBB.1 descendant lineage circulation, antigenic cartography, preliminary preclinical data on

immune responses in animal models, preliminary preclinical immunogenicity data on the performance of candidate vaccines that was provided to us confidentially by manufacturers, and B-cell responses following vaccination or infection.

So I'm just going to show you a few of the highlights. Here's a simplified illustration of the phylogenetic relationships of the clades. And here you see where the Omicron lineage emerged, and it has gradually continued to diversify. So here we have the XBB.1.5, 1.16 up there. And so where we are a year later is that now we're not seeing any evidence of the trajectory flipping back to these earlier variants. All of the variants that are emerging are continuing to do so in essentially linear progression.

Now looking at the variant circulation, on the data above are the numbers, and the data below are percentages of the various lineages. And you can see that XBB.1.5 and 1.16 were dominant globally, but the earlier variants, Alpha, Beta, Gamma, and Delta are no longer detected in humans. I will point out that the actual numbers of isolates is quite a bit lower than at the peak of BA.1 and BA.2 circulation.

So what is the impact of these recent variants on cross neutralization following vaccination? So here we have data, the references down below, data from people that got one dose of a Pfizer vaccine, two doses, or three doses. And I'll draw your attention to this tail end of the x-axis, which is XBB.1. So these are neutralizing antibody titers tested against different variant viruses. And you could see that we essentially don't get cross-reactive neutralizing antibody against the XBB.1 until we've had multiple doses of the vaccine. And even there, many of the data points are at or below the limit of detection.

In this study, looking at a number of different cohorts, and you may have seen some of these data presented differently by Natalie, we're looking at cohorts that got three doses of the

ancestral vaccine, four doses of ancestral vaccine, three doses of ancestral plus a bivalent BA.4/5 lineage vaccine, vaccinated people who had a BA.2 breakthrough, and vaccinated people that had a BA.4/5 breakthrough infection. Again, looking at the y-axis are the neutralizing antibody titers, and on the x-axis are the titers tested against different variants. The far left is the ancestral, and the far right are the XBB and XBB.1. So what we see is that people who had three doses of the ancestral vaccine do not have detectable neutralizing antibodies against the XBB and XBB.1. People that had four doses of the ancestral vaccine, you have just a few exceptions, but as we've given, as we look at sera from people that had three doses of the ancestral vaccine with the bivalent, the fold reduction from the neutralizing titer against the original ancestral strain is reduced down from 155-fold to 85-fold, with breakthrough infections with BA.4/5. Again, you see that.

Here are another set of data from a different citation. Here, we're looking at the top panel at people that got the BA.1 bivalent vaccine. And below are people that got the BA.4/5 bivalent vaccine. On the left-hand side are people that did not have prior infection. And this is tested in terms of nuclear capsid antibody. And on the right-hand side are people with hybrid immunity, so they've had prior infections in addition to vaccination. And so what we see is in that people that have their protection mediated by vaccination alone, we see relatively poor cross-reactivity against the XBB.1 lineage descendants. It's a bit better in people that got the BA.4/5 bivalent vaccine. And it is a bit better in people that had hybrid immunity.

One more study looking at people that got a BA.5 bivalent booster. These are sera 14 to 32 days post-infection comparing people who had no infection history, on the left, and people with an infection history, on the right. Again, reiterating that a lot of people that were vaccinated with the BA.4/5 bivalent vaccine have lower undetectable antibody titers against XBB.1. Some

have low titers with a 35-fold reduction from the ancestral. But in contrast, people that have hybrid immunity have some cross-reactivity.

Now, we really struggled to find the correlation between these neutralizing antibody data and vaccine effectiveness data. The studies are summarized, going down the left are the studies. And we're looking at relative vaccine effectiveness, because of course there are no longer any placebo-controlled studies. So we're looking at relative vaccine effectiveness. The red spectrum are from people that got BA.1 bivalent vaccines, and the blue spectrum colors are people that got BA.4/5 bivalent vaccines. And we're looking at VE against death, severe disease, symptomatic disease, and any infection. So we see that the bivalent vaccines do provide a high degree of protection against death and severe disease, and it gradually reduces when we look at protection from infection.

There was one study from Finland that split the data out in terms of the hazard ratio. So it's the risk of severe disease at two different time periods. The green symbols are hospitalization due to Covid. The blue triangles are deaths due to COVID-19, and the red inverted triangles are deaths in which COVID-19 was a contributing factor. And here the data have been split out over a period where XBB.1 descendant lineages, on the right-hand side, had been circulating. And this is the first evidence that we, the hint that we have, that perhaps the protection or vaccine effectiveness is reduced in a period when XBB.1 lineage viruses were circulated.

You heard already about antigenic cartography. So we look to see where the XBB lineage viruses fall. Here's XBB.1 and XBB.1.5, and they are, again, quite distinct from BA.2. We have limited precision on where these are located, but they're antigenically quite distinct. And now we're looking at the antigenic cartography of the variants using hamster sera. And you can see that XBB.1 is up here, and it's quite distanced from BA.4/5 and BA.1 and 2.

So what about animal data from infection with an XBB.1 descendant lineage virus? And so here, on the left-hand side, are sera from hamsters that were infected with an XBB.1, and on the right-hand side with hamsters that were infected with XBB. And you could see that these sera cross-react well with the different variants, and there's relatively poor cross-reactivity going back towards the older lineage viruses.

There has been a lot of concern about this phenomenon of immunologic imprinting. And so this is a phenomenon where if you have people that have a memory response to the prior vaccination or prior infection, and you then vaccinate with a new antigen, whether you boost, primarily boost the memory response or whether you make new memory B-cells. So here's a lot of information and I will talk you through it slowly. So these are neutralizing antibody titers, and we're looking at the top panel. So these are different cohorts in China from people that received three doses of the inactivated coronavirus vaccine. And then they had a BA.1 breakthrough infection or a BA.2 breakthrough or BA.5 breakthrough or BA.7 breakthrough infection. And in all of these people who were vaccinated with the ancestral inactivated vaccine and then had breakthrough infections, they all had higher neutralizing antibody titers against the ancestral strain than they did against the new variant that they were infected with.

However, when people had two breakthrough infections in a row, you then lost this evidence of immunologic imprinting. So these are people that had a BA.1 breakthrough followed by BA.5 or BA.7, a BA.2 breakthrough followed by a BA.5 and BA.7. So repeated exposure to Omicron lineage viruses, with the repeated exposure to these new antigens, you lose the evidence of immunologic imprinting.

And this last panel here are people that were not vaccinated, but they had a BA.1 or BA.2 infection followed by a BA.5, BA.7. And here you do not see the preferential boosting of the

response to the ancestral strain. Now if you go to the lower panel, we're now looking at how these sera from these last three groups perform in testing against the XBB lineage viruses. So now you're focused on the right-hand four columns of these neutralizing antibody titers, and you can see that there is cross-reactivity in people that had breakthrough or serial breakthrough infections in both instances.

So to summarize the data that we reviewed in our committee meeting, that in the fourth year of the pandemic, there's high seroprevalence in the global population following infection or vaccination, and the immunologic profiles against SARS-CoV-2 are highly heterogeneous. There are people who have been infected with different variants or vaccinated using different platforms. But there continues to be a substantial genetic and antigenic evolution of the spike protein of SARS-CoV-2, and the evolutionary trajectory continues to diverge from the index virus.

Even though there are increasing gaps in genomic surveillance globally, the available data indicates that the index virus and the early variants are no longer detected in humans. As of May of 2023, the XBB.1 descendant lineage is currently predominant globally. These XBB descendant lineages, including XBB.1.5 and 1.16, are highly immune escaped, have escaped immune detection, XBB.1.5 being one of the variants with the greatest magnitude of immune escape from neutralizing antibodies to date.

The estimates of VE against currently circulating variants, including the XBB.1 descendant lineages, are very limited in terms of numbers of studies, vaccine products evaluated, and populations assessed. Some studies showed similar VE against BA.5 descendant and XBB one descendant lineages. While others uc suggest reduced VE during periods of performance of XBB.1 descendant lineages. Sera from people who had received two, three, or four doses of

index virus-based vaccines or a booster dose of a bivalent, either BA.1 or BA.4/5 mRNA vaccines, showed substantially lower neutralizing antibody titers against XBB descendant lineages as compared to titers specific for the antigens included in the vaccines. And of course, people with hybrid immunity due to any SARS-CoV-2 infection showed higher neutralizing antibody titers against the XBB descendant lineages as compared to those who were vaccinated with no evidence of infection.

There's in vitro evidence of immune imprinting that may be occurring, but based on observational epi data, epi studies to date, the clinical impact of this remains unclear. We saw preclinical data shared confidentially by vaccine manufacturers that showed that vaccination with XBB.1 descendant lineage containing candidate vaccines, including XBB.1.5, elicited higher neutralizing antibody responses to currently circulating variants compared to currently approved vaccines.

We acknowledge limitations of the available evidence. We had the timing, specific mutations in antigenic characteristics, and the potential public health impact remain unknown. The majority of available preclinical and clinical responses are to XBB.1 and 1.5, and minimal data on any of the other variants. The data on immune responses over time following infection are limited. The data on immune responses specific for XBB.1 descendant lineages are largely restricted to neutralizing antibody and are limited for other aspects of the immune response, including cellular immunity. Data on protection conferred by hybrid immunity are largely derived from populations that received mRNA booster vaccines. Data on VE, on current Covid vaccines, including index-based and bivalent, against XBB descendant lineages were limited. And estimates during periods of XBB.1 descendant lineage circulation were only available for

the mRNA vaccines. Data on candidate vaccines that include an XBB.1 descendant lineage were limited to animal models.

So we recommended that in order to improve protection, in particular against symptomatic disease, new formulations of COVID-19 vaccines should aim to induce antibody responses that neutralize XBB descendant lineages. Again, I'll emphasize that our focus is on achieving breadth of immunity. So one approach that we recommended was the use of a monovalent XBB.1 descendant lineage, such as XBB.1.5, as a vaccine antigen. And given the small genetic and antigenic differences from XBB.1.5, XBB.1.16 may be an alternative. And other formulations or platforms that achieve robust neutralizing responses against XBB descendant lineages could also be considered.

While currently approved COVID-19 vaccines, including those based on the index virus, continue to provide protection against severe disease, our committee advised moving away from the inclusion of the index virus and future formulations of COVID-19 vaccines for a couple of reasons. First, the index virus and antigenically closely related variants no longer circulate in humans. The index virus antigen elicits undetectable or very low levels of neutralizing antibodies against currently circulating variants, including XBB descendant lineages. The inclusion of the index virus in bi- or multivalent vaccines reduces the concentration of the new target antigen as compared to monovalent vaccines, and this may decrease the magnitude of the humoral immune response. Immune imprinting due to repeated exposure to the index virus may actually reduce the immune response to new target antigens. But as I pointed out, the clinical correlation of this is not clear.

So with that, I think I will close and thank you for your attention, and see if you have any questions.

Q & A

Dr. Monto: Thank you, Dr. Subbarao, for a very broad and helpful explanation of where we are right now. I'm getting the feeling that we are moving towards the situation we usually have with influenza, where it's very difficult, given different manufacturing approaches, to come up with a strain-specific recommendation. That we are going towards something like a 'like' recommendation, giving the manufacturers a bit of a choice. Is that where we are going now?

Dr. Subbarao: So one difference from what we do in influenza is in the case of influenza, we actually name strains. And we've attempted to do so because we want to make sure that if we say XBB.1.5, that people know what that consensus sequence should look like. I don't have a huge amount of confidence that we have really understood the cadence of this evolution. And so our committee is planning to meet twice a year, about six months apart, to review the data and to see whether, in fact, an update is needed or not needed. So I think it's, I'm still not sure exactly where we are with flu. But we certainly, there are some commonalities.

Dr. Monto: Thank you. Dr. Perlman.

Dr. Perlman: Thank you, Kanta, for a great presentation. So I have one comment and one question. So this whole issue of leaving out the ancestral strain, it depends on it not circulating, particularly for children zero to 23 months, who may not be exposed to the virus previously. So with the decreased testing around the world, how are we? I think that could potentially be a problem, which I think you would agree with. But the question I had was, looking at these different variants, the XBB.1.5 and .16 and the, and XBB.2.3, one of our questions is which one should be in the formula? And you're, the WHO, is addressing the same question, but it looks to me like they're so close that it may be an unanswerable question. Because the differences could be out of the spike protein completely. Even if you have less efficacy, it may be because of an ORF9B or some other protein. So how are you guys approaching that?

Dr. Subbarao: Right, so I'll take your comment first. And that is about how confident are we that the ancestral strain and its related, early variants are truly not circulating. I think we are quite confident that they are not circulating. Certainly surveillance has changed over time, but we are not seeing any evidence of those viruses circulating. And the only age group in which that would be a problem would be the very young, because almost everybody else, because of, you know, the evidence I've shown you on seroprevalence, would have a memory response to the older strains.

The second question is about how related these are. So I think I'd really want to emphasize that, unlike the way we people think we do this for flu, we really want to achieve the breadth of immunity that would cover these strains. And you could see that they are quite related. And so we're trying to achieve breadth that would cover the XBB.1 descendant lineages. And I think that to me is more important than sort of saying exactly which. So we're not trying to match exactly what's going to circulate. We want to provide the breadth of immunity that covers that class of viruses.

Dr. Monto: Thank you. And I just want to point out to the committee that Dr. Subbarao is not going to be available this afternoon when we get into our general discussion. So if you have any additional questions that you'd like to ask her please do so now in the next couple of minutes. Dr. Levy.

Dr. Levy: Thank you, Dr. Subbarao, for a great presentation. You elegantly reviewed WHO's assessment of the variants and the antibody response to the different variants and how those do or do not match up. My question to you relates to correlates of protection. This has been an ongoing issue. How well do we know those correlates? Obviously, antibodies are important and are well worth measuring. They're not the whole story. Dr. Offit made a comment earlier

today, which I agree to as well, has WHO considered any T-cell based immunologic data in analyzing the situation? And what do you learn? What do we learn from that?

Dr. Subbarao: Yeah, no, I think that's a —

Dr. Levy: And, I'm sorry. And then specifically around the issue of any potential value of including the original index strain. You're very clear in your recommendation that you don't think that's indicated at this point, but does the T-cell data speak to that point as well? Thank you.

Dr. Subbarao: Thanks. So I think that we all acknowledge that neutralizing antibody is a very important correlative protection, but it doesn't tell the whole story, because as we see in repeated data sets, that there's very poor neutralizing activity against the XBB descendant lineages induced by the ancestral vaccine, and yet there's good protection against severe illness and death. So clearly, other arms of the immune system are playing a role there. We do not have a lot of data on understanding the mechanisms for that protection. And I really can't point to a lot of information that provides that. There is a gap.

Dr. Levy: Got it. And is WHO advocating that for the future, to capture more of this T-cell data?

Dr. Subbarao: Absolutely. Absolutely.

Dr. Levy: Is WHO on record with that?

Dr. Subbarao: So there are different parts of the WHO committees, including the Technical Advisory Group on Virus Evolution as well as TAG-CO-VAC, but we would certainly encourage ongoing studies to try to understand this.

Dr. Levy: Thank you.

Dr. Monto: Thank you. Dr. Chatterjee.

Dr. Chatterjee: Thank you, Dr. Monto. Dr. Subbarao, thank you very much for your presentation. I have a comment and a question. The comment is regarding chasing variants, if you will. So we know that this virus continues to evolve, and it doesn't seem to be reverting towards the ancestral strain and evolving from its current status. Obviously where we are today is most likely not going to be where we will be a few months from now when the vaccines will be deployed. And so we've talked in the past about not trying to chase variants, but it seems like that's where we find ourselves now.

My question related to that is about the conserved areas on the virus that don't appear to be undergoing so much change. And if any work is being done to prepare vaccine candidates based on those. Could you address that?

Dr. Subbarao: Sure. So I think that is an area of great interest to find conserved portions of the spike protein, or conserved, that would elicit more broadly cross-reactive immunity. And there certainly are elements of the spike that are conserved. There's a lot of effort, I see more in the space of the monoclonal antibodies, for instance. And so, but I think in terms of, I don't see them coming into focus particularly yet for vaccines that are in current use. So it's still in a research space. And I think that that is something, you know, we have a parallel of this in influenza as well, looking at the HA stem, for instance. So there are conserved portions of the spike that are being explored by people with monoclonal antibodies and in the research space. But if you have a spike, a full spike protein, you would expect that you would induce immunity against different portions of the molecule.

Dr. Monto: Thank you.

Dr. Chatterjee: Dr. Monto, could I ask a follow up question?

Dr. Monto: Well, a very short follow up question.

Dr. Chatterjee: Very quick follow up.

Dr. Monto: We're already late.

Dr. Chatterjee: Dr. Subbarao, you mentioned that your committee is planning to meet approximately every six months. Should we expect recommendations for modification of the vaccine candidate in six months' time?

Dr. Subbarao: It's going to be entirely data driven. We are going to meet every six months to review the data. There may be no update, there may be an update. We will just see how the data turn out.

Dr. Chatterjee: Thanks.

Dr. Monto: Thank you. Dr. Meissner.

Dr. Meissner: Thank you, Dr. Monto. And thank you very much for that presentation, Dr. Subbarao. I have a question for you specifically. Can you comment on your opinion regarding the importance of standardizing the vaccines from a global perspective?

Dr. Subbarao: So the WHO's very concerned about making sure that vaccines are available for the entire population. Not, and I know that the VRBPAC is meeting specifically about the United States. So we have met with a number of manufacturers that have different platforms to try to make sure that the message goes out that our recommendations apply to all platforms.

Dr. Monto: Thank you. I think we all hope we can standardize as much as possible. Things are difficult enough as they are in terms of trying to figure out past histories of vaccination, et cetera. Dr. Kim.

Dr. Kim: Thank you, Dr. Subbarao. That was a terrific discussion. A simple question. I don't know if you have if you have data that you might be able to pull to respond to

this question, but do we have information on geographic or population-based changes that might be taking place that might give us a hint of the leading edge of the evolution of the virus?

Dr. Subbarao: So all I could say is that there's a separate committee at the WHO called the TAG-VE that monitors virus evolution. And they have a risk assessment framework now. And so they look at new variants as they emerge and their impact on diagnostics, therapeutics, and vaccines. And then it comes to our committee, specifically on vaccine composition. So we're all part of a system that sort of looks at different aspects, and communicate with each other.

Dr. Kim: But at this point we don't have anything that might give us a hint of where the direction that that the virus might go?

Dr. Subbarao: Not really. I think what we're more confident of than we were a year ago is that the trajectory is essentially linear. And the WHO is working hard to make sure that that there is sufficient surveillance, say sentinel surveillance, in different parts of the world, so that we do actually have some monitoring capability.

Dr. Kim: Thank you.

Dr. Monto: Thank you. Going to call on Dr. Nelson and then Dr. Hawkins. And then we are going to let Kanta get back to her regular activities. Dr. Nelson.

Dr. Nelson: Thank you, Dr. Monto. Mike Nelson, University of Virginia. I want to thank you for that very elegant presentation and particularly the insightful impact of the immune imprinting on your deliberations. So you certainly address the selection piece of what should go in a vaccine. I would like to ask whether the WHO was under the assumption that the vaccination would be occurring on an annual basis as the posture we've adopted here in the United States. And the second question would be, were there any particular factors that the TAG-CO-VAC in

their deliberations identifies as key factors for literally not selecting the latest emerging strain that's circulating throughout the world?

Dr. Subbarao: So that's two parts. So the first part is, can you remind me what the first was?

Dr. Nelson: Yeah. Was it the assumption on an annual vaccination? You're meeting twice a year.

Dr. Subbarao: Yes.

Dr. Nelson: The question came up, are you going to change it midyear. Seeing to raise the question to me, is it really going to be administered more than once a year?

Dr. Subbarao: No, I think —

Dr. Nelson: Or is it the recommendation —

Dr. Subbarao: I think, yes. So the reason we're meeting twice a year is because I think the temperate climates of the Northern Hemisphere seem to have, you know, sort of decided that they will do a fall campaign. But the WHO's recommendations are for the whole world. And so we do want to make sure that we're monitoring what's happening for the tropical belt as well as the southern hemisphere. And so that's the reason for the twice a year discussion. We, this committee is very strictly in the lane of recommending the vaccine antigen composition. There's a different part of the WHO that is sage, and of course, each country has their own regulatory authority that decides when vaccine is used. So our committee does not comment on that. We are just going to review the data on an ongoing basis, no less than twice a year. May have to do it more often than twice a year.

Why would we not go with the most recent virus? Because I do believe that we need some data on antigenic cartography. We need to know how distant it is. We need to know a little bit about the performance of the of that particular spike, either in infection or vaccination, at least

from preclinical data. So I don't think we'll ever be in a situation where we could just jump on the most recent one, because we don't actually know how different it is from something that we know a lot more about. And so I would like us to continue to have some confidence from the data, that we have a sense of what's happening with, say this XBB.1 descendant lineage, for instance.

Dr. Monto: Thank you. Dr. Hawkins.

Dr. Hawkins: Yes, thank you very much. And this is a follow-up on comments by Dr. Meissner regarding global protection. I may have misread the slide early on. And this was about data available in Asia and Africa. It appeared that there was some areas of no data. If that was accurate, can we use the information that WHO was providing regarding recommendations for the rest of the world?

Dr. Subbarao: Yeah, so there are certainly, I mean, the WHO is in the process of setting up what they're calling CO-V-NET to make sure that sort of, like the global Influenza program has laboratories that are on the ground that then report to reference laboratories, and so on. So they're still in the process of doing that. I think what we have for the time being is collection of information that different organizations are generating on their own. So this is not, this is much less of a sort of network that WHO necessarily controls. They can encourage. And so we certainly have gaps in data. And the WHO is trying to address this by developing this CO-V-NET system.

Dr. Hawkins: Thank you.

Dr. Monto: Thank you. And now we're scheduled for a break, and we're running a bit late. Can we start, Sussan, at 11:15 instead of 11:20? In other words, can we have a 10 minute break?

Dr. Paydar: Yes, Dr. Monto, I trust your judgment.

Dr. Monto: Okay. 11:15 Eastern, we return.

Moderna Presentation — Moderna COVID-19 Variant Vaccines

Dr. Monto: Welcome back. We now have three presentations from the vaccine manufacturers. First, we're going to start with a presentation from Moderna. The group there is led by Rituparna Das. So, over to you, Dr. Das.

Dr. Das: Thank you, Dr. Monto. Good morning. My name is Rita Das, and I'm the Therapeutic Area Head for Respiratory Vaccines at Moderna. As the pandemic has evolved, Moderna has continued to monitor emerging variants to ensure we are prepared to develop and evaluate new COVID-19 vaccines. We are committed to generating preclinical and clinical data to share with agencies worldwide to inform vaccine update decision-making. Additionally, we maintain manufacturing readiness to supply new vaccines as the need arises. Accordingly, we support a harmonized recommendation by FDA and this committee, WHO, and other agencies around the world.

Today we will show you the results of our effectiveness study of the authorized BA.4/5 bivalent vaccine, which compliments the work that others have presented today. We will also show you the cross-neutralization ability of the BA.4/5 vaccine for the XBB subfamily of variants. Finally, we've developed investigational XBB.1.5 and XBB.1.16 containing vaccines. We'll be sharing preclinical data on both, as well as clinical data on the XBB.1.5 containing vaccine.

So let me begin with an update on the effectiveness of the currently authorized BA.4/5 bivalent vaccine from an ongoing study in collaboration with Kaiser Permanente Southern California, a health system that covers 4.6 million people. The preprint for these analyses was posted to Med Archives earlier this week. We initiated this study to monitor the effectiveness of

the original Moderna COVID-19 vaccine in 2020. The study protocol has subsequently been modified to monitor the effectiveness of the Moderna BA.4/5 bivalent vaccine since its authorization in 2022.

Study uses a matched cohort design with three groups. First, individuals who have received the BA.4/5 booster after at least two doses of any mRNA vaccine. Then, individuals who have been vaccinated but have not received the BA.4/5 bivalent booster. And finally, individuals who have not been vaccinated for Covid at all. The participants in these groups were matched on age, sex, race, and ethnicity, and the index date, the vaccination date for the bivalent cohort. Use of the bivalent BA.4/5 vaccine was captured from late August through the end of December of 2022, and follow up was captured through January, through the end of January of ‘23.

There are two planned comparisons for effectiveness in this study. First, the comparison between those who received the BA.4/5 bivalent booster and those who were vaccinated but did not receive that booster. This is the relative effectiveness comparison. Next, the comparison of the BA.4/5 bivalent booster recipients to those who received no COVID-19 vaccine. This is the absolute effectiveness comparison. Based on the continued sequencing of incident cases in the study, here's the distribution of SARS-CoV-2 variants from August ‘22 to January ‘23. The predominant variant during the observation period of this study was BA.5, shown in dark blue. During January, the last month of collection of data for this analysis, there was some representation of XBB, shown in orange, and this was mostly XBB.1.5.

Here are the baseline characteristics of the participants in the three cohorts. Age was similar in all cohorts. There was significant representation of non-white races. And among the bivalent vaccine recipients, many had received a vaccine as a fourth or fifth dose. In the original

vaccine group, most had received the vaccine as a third or fourth dose. The time since the last dose was shorter in the bivalent group.

Moving now to the vaccine effectiveness results. Recipients of a bivalent booster demonstrated a relative vaccine effectiveness of 70% against chart-confirmed hospitalizations for COVID-19, which was the primary endpoint for the study, compared to those who had received the original mRNA vaccine. Relative effectiveness against COVID-19 deaths was 83%, and relative vaccine effectiveness for ED or urgent care visits was 55%. On the right, the absolute vaccine effectiveness numbers were high, 83% for hospitalization, 90% for deaths, and 55% for ED or urgent care visits.

These data confirm that during the BA.5 wave in the US, the Moderna bivalent COVID-19 vaccine protected vaccinated individuals against hospitalizations and deaths from COVID-19, and as well as from ED and urgent care visits from the illness. I'll now turn the presentation to Dr. Darin Edwards, who will discuss our variant monitoring and preclinical evaluation of new vaccine candidates.

Dr. Edwards: Thank you, Dr. Das. My name is Darin Edwards and I'm Executive Director, Program Leader of COVID-19 Vaccines at Moderna. We continuously monitor for emerging variants and classify them based on three factors, incorporation of immune-evading mutations, their measured growth dynamics, and global and region-specific coverage. In this process, we group antigenically similar lineages, as antigenic coverage does not always require an exact sequence matching. For emerging variants that are growing rapidly, 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. These efforts are performed to allow for expedited delivery of new vaccines as they are requested.

As was also presented by the CDC earlier today, in most regions, the XBB sublineage is dominating, with XBB.1.5 the most dominant. However, it is important to highlight that the XBB sublineage is comprised of several cocirculating variants and continues to evolve. We group XBB variant viruses into a common subfamily based on antigenic similarities seen in their spike proteins. Each circle in this Venn diagram shows the total number of mutations for XBB.1.5 and XBB.1.16 versus the ancestral virus. The number one on the left and the number two on the right identify that, in total, there are only three unique mutations between these XBB variants. The overlapping section of the Venn diagram in dark orange indicates 41 mutations differ from the ancestral virus but are shared between XBB.1.5 and XBB.1.16.

In contrast, the Venn diagram on the right shows there are 15 unique mutations on BA.1 and 13 unique mutations on BA.5 that are not shared between these two variants. The overlap in the middle highlights that there are only 21 mutations in common between these two variants versus the ancestral virus. It's important to highlight that BA.1 and BA.5 would not have been grouped into a common subfamily based on their antigenic differences. This type of analysis provides the basis for a variant planning strategy.

Here is a comparison of the antigenic differences between XBB subvariants and BA.5, a component of the currently authorized vaccine. XBB.1.5 is on the left and XBB.1.16 is on the right. Significant antigenic differences were found with XBB.1.5, differing from BA.5 by 20 mutations, while XBB.1.16 differs from BA.5 by 23 mutations. This level of antigenic change, especially in key sites of known neutralization in the receptor binding domain and the N-terminal domain suggests that XBB sublineage viruses have evolved to significantly evade immunity provided by prior Omicron infection or the currently authorized BA.5 bivalent boosters. This suggests that an updated vaccine composition may be needed.

Next, we will show that these antigenic differences may contribute to decreased cross-neutralization of XBB variants. In participants without and with prior infection, sera collected after vaccination with the BA.4/5 authorized booster were assessed for neutralization against BA.4/5 and XBB subvariants. As shown in the blue on the left, titers against BA.4/5 were quite robust in both cohorts, while neutralization against XBB.1.5 variant, shown in orange on the right, was detectable but considerably lower. This also may provide a rationale for the real-world effectiveness data, which shows reduced protection from BA.4/5 bivalent vaccine when XBB family subvariants predominate.

The XBB sublineage continues to evolve over time, with newer subvariants emerging in specific geographical regions, including XBB.2.32, which has now emerged in several countries, including the US. Here we see the antigenic differences between XBB.1.5 and XBB.1.16 on the left, XBB.1.5 versus XBB.2.32 in the middle, and XBB.1.16 versus XBB.2.32 on the right. Again, limited antigenic differences are noted between these three different subvariants of XBB. Of note, XBB.1.91, which is also circulating, and XBB.1.5 have identical spike proteins. This analysis suggests that cross neutralization of the XBB subfamily is not likely to be significantly impacted regardless of which specific XBB variant is selected for inclusion in an updated 2023 fall Covid vaccine composition.

And now I would like to walk you through preclinical studies of investigational XBB monovalent and bivalent subvariant containing vaccines. These vaccines are developed and evaluated in mice as primary series and boosters to confirm that they are immunogenic in naive and previously vaccinated animals and to evaluate the breadth of immunity across variants. Both primary two dose vaccination studies as well as booster studies were performed, with booster vaccination assessed in mice previously immunized with a two-dose series of our original

vaccine. Investigational vaccines for monovalent XBB.1.5 or XBB.1.16 as well as bivalent vaccines comprised of BA.4/5 plus XBB.1.5, or BA.4/5 plus XBB.1.16, have been developed and are in the process of being evaluated.

Now I'll show you neutralization titers in mice vaccinated with a primary two dose series of the BA.4/5 bivalent vaccine versus monovalent XBB.1.5 and the BA.5 plus XBB.1.5 bivalent vaccine. Here are the neutralization titers for the BA.4/5 bivalent vaccine against BA.4/5, XBB.1.5, XBB.1.16, and XBB.2.32 viruses, all listed on the x-axis. We saw high levels of neutralization against the BA.4/5 virus but limited neutralization of the XBB sublineage viruses. In contrast, XBB.1.5 containing vaccines demonstrated high levels of neutralization against XBB sublineage viruses. It is important to highlight that XBB.1.16 and XBB.2.32 were effectively neutralized by both XBB.1.5-containing vaccines. Next, I will describe the neutralization titers from our booster study comparing the same investigational XBB.1.5 containing vaccines. Neutralization was assessed prior to the booster dose, as shown with the hash lines, and after, shown with the solid colors. On the x-axis are the variants BA.4/5 and XBB viruses. The fold increase in titers measured after the boost compared to the pre-boost titer is listed below the graphs. Both XBB.1.5 containing boosters increased neutralization against XBB subvariant viruses to levels higher than the BA.4/5 booster with minor differences in neutralization measured between XBB.1.5, XBB.1.16, and limited reduction versus XBB.2.32.

Next, I will describe the neutralization results from our booster study comparing XBB.1.16 containing vaccines. Both investigational XBB.1.16 containing boosters increased neutralization against XBB subvariant viruses, with 11- to 33-fold increased neutral neutralizing antibody titers measured after the boost. As seen in the previous booster study with XBB.1.5

containing vaccines, only minor differences in neutralization were measured between XBB.1.5, XBB.1.16, and XBB.2.32 viruses.

In summary, preclinical data suggests that an XBB containing vaccine is more immunogenic against currently circulating XBB variants than the authorized BA.4/5 bivalent vaccine. Consistent with the minimal antigenic differences seen across the XBB subfamily, cross neutralization across the XBB sublineage for both XBB containing vaccines was demonstrated. And now I'll turn it back to Dr. Das to describe results from our clinical assessment of the investigational XBB.1.5 variant containing vaccines.

Dr. Das: Thank you, Dr. Edwards. In the interest of providing data for the strain selection process, we performed a clinical study in which 101 participants were randomized to receive either a monovalent XBB.1.5 vaccine or a bivalent BA.4/5 plus XBB.1.5 vaccine. The total dose for each vaccine was 50 micrograms. All of the study participants previously received four doses of vaccine, a two dose primary series and booster of the original vaccine, plus any BA.4/5 mRNA bivalent booster vaccine three or more months prior to enrollment in the study. All analyses from the study are descriptive.

The characteristics of the recipients of the monovalent and the bivalent vaccine were generally balanced. The median age was approximately 50 years, and there was representation of individuals above 65 in both groups. The number of participants with prior SARS-CoV-2 infection was approximately 70% in both groups.

This slide shows the neutralization titers against XBB.1.5 from the two vaccines. The monovalent XBB.1.5 vaccine is in orange, and the bivalent XBB.1.5 vaccine is in green. Both vaccines induced robust XBB.1.5 neutralizing responses. The GMT and fold rise for the monovalent vaccine was numerically higher than that seen for the bivalent vaccine. And here on

the right are the cross-neutralization titers against XBB.1.16 from both XBB.1.5 vaccines. Again, both vaccines induced robust XBB.1.16 neutralizing responses, and the titers were numerically higher for the monovalent vaccine. For each vaccine, the neutralization titers against XBB.1.5 and XBB.1.16 were similar, and this is expected given the antigenic similarity between these two XBB variants.

Here are the same data, now separated by prior SARS-CoV-2 infection status. As we've seen previously, the post-boost titers are numerically higher in the SARS-CoV-2 positive group. But this analysis confirms overall that administration of an XBB.1.5 containing vaccine provides a substantial increase in XBB.1.5 and XBB.1.16 responses regardless of history of prior infection. We also tested the sera from the monovalent and bivalent XBB.1.5 vaccines for cross neutralization against BA.4/5, as well as the ancestral strain, D614G. The pre-boost titers against BA.5 were high since everyone had received a bivalent booster, but there was still a rise after vaccination with the XBB.1.5 containing vaccine. The pre-boot titers, on the right now, against the ancestral strain were also high, and there was still a rise after vaccination.

Now, the titers against BA.4/5 and the titers against ancestral strain were similar with either the monovalent or the bivalent vaccine. Now note that the ancestral titers are no longer the highest titers observed despite everyone in the study having received multiple doses of the ancestral strain. This observation is promising because it indicates that it may be possible to retrain immunity with updated vaccines.

As has been discussed earlier today, the XBB.2.32 subvariant has recently emerged and is increasing in circulation. Using our research assay, we were able to quickly assess the neutralization patterns against XBB.2.32 in a randomly selected subset of 20 participants from the XBB.1.5 monovalent vaccine recipients in our clinical study. The XBB.1.5 monovalent

vaccine elicited similar and robust neutralizing antibody titers against XBB.1.5, XBB.1.16, and XBB.2.32, further demonstrating the ability of the XBB.1.5 monovalent vaccine to cross neutralize multiple XBB variants.

We are also showing here the breakdown of the random subset analysis by baseline. SARS-CoV-2 status across the variants in the research assay. The same trend is seen, with numerically higher GMTs for baseline positive participants. Overall, this analysis shows that, again, administration of the XBB.1.5 monovalent vaccine provides a substantial increase in XBB.1.5, XBB.1.16, and XBB.2.32 responses regardless of prior infection.

Now we'll move to the safety of the vaccines. Again, the monovalent vaccine is in orange, and the bivalent vaccine is in green. This slide shows the solicited local reactions. Both vaccines were well tolerated. Pain was the most frequent local reaction, and all other reactions were very low. For reference, here, the local reactions from the original booster, in light blue, and the BA.4/5 bivalent in dark blue. You can see that the local reactions across all vaccines are generally similar. Here are the systemic reactions reported post vaccination. Headache, fatigue, myalgia, and arthralgia are the most common reactions. Systemic reactions are also similar for both monovalent and bivalent XBB.1.5 containing vaccines, and there are very few grade three reactions and no grade four reactions. Again, the systemic reactions for the prior vaccines shown in the bottom panel are consistent. There have been no serious AEs, deaths, or AEs leading to discontinuation in our current study.

So with that, I would like to summarize the data we have shown you today. The BA.4/5 bivalent vaccine was highly effective against COVID-19 hospitalizations, death, and ED and urgent care visits over the ‘22-’23 period when BA.5 was predominant. The antigenic similarities in the XBB variants support the subfamily grouping of these variants. We also evaluated XBB

containing vaccines in both preclinical and clinical studies. Preclinical data suggests that an XBB containing vaccine is more immunogenic against currently circulating XBB variants than the authorized BA.4/5 bivalent vaccine. Our clinical study demonstrates that XBB.1.5 containing vaccines elicit robust cross neutralizing antibodies against all XBB variants. The neutralization titers generated by the XBB.1.5 vaccines are very similar against XBB.1.5, XBB.1.16, and XBB.2.32. The safety profile of the variant containing vaccines continues to be very similar to the previously authorized vaccines, both the original COVID-19 vaccine as well as the bivalent.

We confirm that Moderna is prepared to provide adequate supply of a new variant containing vaccine for fall of 2023 based on the recommendation made today by the FDA. Thank you very much to the committee for the opportunity to present. We also thank our investigators, study site personnel, and all the individuals who participated in the trials. We are very happy to address any questions.

Q & A

Dr. Monto: And thank you for keeping right on time. Questions? We have a few minutes for questions here. Dr. McInnes.

Dr. McInnes: Thank you, Arnold. I have a question for Moderna. So, do you have an independent epidemiological program about viruses that are causing disease, or are you purely respondent to CDC through FDA on what you should make? So, you know, I guess I've been in this business a long time, and there are different models .So do you view yourselves as a collaborator in identifying the strains that are causing disease or the, you know, lineages that are causing disease? Or are you just a recipient of data and then you try to respond to that?

Dr. Das: So we do have our own independent surveillance program. We conduct the surveillance so that we can very quickly, as Dr. Edwards mentioned, identify which variants are

becoming more prominent and which variants deserve the preclinical and sometimes clinical evaluation. But in conjunction with what we do, for instance, prior to this meeting, we've had multiple meetings with a lot of the folks on the call here, with a lot of regulatory agencies around the world, so that that line of bidirectional communication is open.

Dr. McInnes: So, sorry Arnold, to follow up. So you have your own independent surveillance that you then feed into WHO, to the FDA, I mean, other authorities, whatever? Is that what you're saying?

Dr. Das: Yes. We do do our own independent surveillance, and we are, you know, we are very happy. And we routinely share our surveillance data globally.

Dr. McInnes: So it's interesting. It's not —

Dr. Monto: So Pamela, we've got a hard stop because of the Open Public Hearing, so.

Dr. McInnes: I hear you, Arnold. I just, I want to determine what Moderna is doing with regard to —

Dr. Monto: Okay, go ahead.

Dr. McInnes: I've asked the question, I want to understand what they're doing independently for surveillance, because it's not that they're short of resources, so I want to be sure what contribution is coming in.

Dr. Das: I mean, we have epidemiologists in Moderna. We have clinical epidemiologists as well as research epidemiologists. They are looking at the tools and doing the surveillance, as I mentioned. We're also doing, we're continuing to sequence in our Kaiser study. We are looking at all of those data together, and so we're looking at publicly available data and data that we are also getting from our studies.

Dr. McInnes: Thank you.

Dr. Monto: Okay, Dr. Perlman.

Dr. Perlman: Yeah. So I have a technical question. So, when you make these new vaccines, the S proteins from these different viruses are a little different. Some of them seem to tend more towards the surface, some of them in the endosome. Do you monitor for levels of S protein expression? Clearly the responses are very nice, but are there differences? Do you ever have to tweak the dosage that you're using?

Dr. Das: So, not the dosage. But we do, you know, because we like to, our goal is to keep the dosages very similar, because we want this to be a seamless kind of replacement process. And now we've shown that the safety is very consistent. We've had about 10,000 people receive variant vaccines in our clinical trials. We do monitor, we generate kind of several candidate sequences, and we monitor the expression levels and then choose a final sequence.

Dr. Perlman: And are there differences between the variants?

Dr. Das: Not very much. Not very much that we've seen.

Dr. Perlman: Thank you.

Dr. Monto: Thank you. We're going to have to move on. As I said, we've got a hard stop because of the Oral Public Hearing. So now we're moving to Pfizer. The presentation is going to be led by Dr. Kena Swanson. Dr. Swanson.

Pfizer Presentation — 2023-24 COVID-19 Vaccine Formula: Pfizer/BioNTech Clinical and Preclinical Supportive Data

Dr. Swanson: Thank you, Dr. Monto. And good morning to the committee. My name is Kena Swanson, and I am Head of Viral Vaccines R&D at Pfizer. On behalf of both Pfizer and BioNTech, it is my pleasure to provide an overview of the recent data that aims to support selection of the vaccine composition for the upcoming fall/winter season. For today's

presentation, I will focus on both humeral and cellular immunity data from our Omicron BA.1 and BA.4/5 modified vaccine clinical studies and learnings from preclinical evaluation of updated vaccine compositions representing more contemporary SARS-CoV-2 variants. Then, I will end the presentation with an update on our plans for supply of the vaccine.

As you already heard earlier today, the XBB sublineages of Omicron continue to dominate the SARS-CoV-2 variant landscape, with XBB.1.5 being the most dominant in the US since February of this year. Continued monitoring of sublineage proportions has shown an increase in other XBBs, indicated by the chart on the left, with XBB.1.16 showing potential to be the next variant to displace XBB.1.5. The group categorized as 'others' in this analysis includes a collection of other sublineages that differ slightly in the spike sequence but individually remain at overall low levels. And as indicated on the right, and as you heard in the prior presentation, the most predominant strains within XBB.1.9 are also increasing, but do not differ from the XBB.1.5 in the spike amino acid sequence. XBB.1.16 and XBB.2.3 differ from 1.5 by only two or three amino acid substitutions, respectively. Later in the presentation I will share data to better understand if these sequence differences translate to any immunological differences.

Importantly, the antigenic distance of these XBB sublineages from the earlier Omicron BA.5 is even more so than the distance of Omicron BA.5 was from the original SARS-CoV-2. The vaccine update to the bivalent Omicron BA.4/5 vaccine in 2022 showed that more closely matching circulating strains offered improved protection against COVID-19. On the right are data from the CDC showing improved effectiveness of the bivalent vaccine against COVID-19 hospitalizations compared to individuals that received the original monovalent vaccines. Data from younger adults are shown above and for adults 65 and older, shown below. With the emergence of the more antigenically distant XBB sublineages and longer time since the booster

dose, the vaccine effectiveness has notably waned from approximately 60% absolute VE to less than 30%. Collectively, the data support that variant-adapted vaccines improve protection, and that an updated vaccine, likely more closely matched to the circulating XBBs, is warranted.

We are still early in the understanding of SARS-CoV-2 evolution and potential seasonal cycles. However, disease activity may be settling into a more typical pattern of peaking during the winter months. Shown on the left is a heat map of data from the from Northern Hemisphere countries, with blue indicating the peak of COVID-19 hospitalizations, all occurring during the typical winter peak observed for other seasonal respiratory viruses, such as those shown on the right for influenza, RSV, and the endemic human coronaviruses.

Now I would like to focus on relevant immunogenicity data from our prior clinical studies evaluating Omicron-adapted vaccines. We have previously shown superior Omicron neutralizing responses with Omicron-adapted vaccines compared to the original vaccine as a fourth dose booster, which aligns with the real-world observations showing variant-adapted vaccines provide increased protection against circulating strains and can restore waning immunity. For today's presentation, I will share an expanded characterization of the humoral response against more recent Omicron strains, as well as characterization of the memory B-cell response, and finally, a view into the T-cell response. In brief, both monovalent and bivalent Omicron adapted vaccines recall spike-specific memory B-cells that recognize epitopes shared between the wild type and Omicron spike and can induce Omicron specific B-cells. We also see clear expansion of both CD4 and CD8 T-cell responses following a variant adapted booster.

First, let's review the clinical and preclinical experience we have gained for variant-adapted vaccines and the importance of these data to inform vaccine composition. Collectively, these data sets have aligned well when evaluating the overall variant immune response profile as

new SARS-CoV-2 variants have emerged. Now I will show results from an evaluation of the neutralizing activity of the current bivalent BA.4/5 vaccine against Omicron XBB.1.5 and 1.16.

Here we show a descriptive analysis comparing the bivalent and original monovalent vaccine neutralizing activity against Omicron XBB.1.5, shown on the left, and 1.16 sublineages, shown on the right, from a subset of participants greater than 55 years of age using a SARS-CoV-2 fluorescent focus reduction neutralization assay. In each data set, Omicron BA.4/5 was included as an internal control, as these were separate testing runs. These data are from the same set subset of participants that were previously used for XBB.1 neutralization data that was published in January of this year. Data are shown for participants with or without prior infection at baseline. Improved responses were observed with the bivalent vaccine, in purple, compared to the original vaccine, in blue, regardless of prior infection status. Similar neutralizing activity was shown for both XBB sublineages. However, GMTs were much lower compared to the vaccine-matched Omicron BA.4/5.

These data are in agreement with effectiveness data showing that Omicron based vaccines can provide improved protective immunity against Omicron sublineages. However, lower XBB titers reflect the greater antigenic distance of the current strains. It is important to note that because XBB.1.5 has a spike sequence identical to the predominant XBB.1.9 strains, data for 1.5, shown here, should reflect activity against 1.9.

Next, B-cell responses were evaluated in a subset of individuals who received three prior doses of the original BNT162b2 vaccine and were then boosted with the bivalent Omicron BA.1 vaccine as a fourth dose. The participants evaluated in the study were SARS-CoV-2 naive at the time of the BA.1 booster was administered. As shown to the right, a flow cytometry-based method using distinctly labeled wildtype and Omicron and BA.1 spike proteins as probes was

used to detect memory B-cells specific to either type epitope, shown in blue, or to Omicron epitope, shown in green, and finally, those specific to shared surface epitopes between both wildtype and Omicron spikes, noted in the top right in orange. Overall, the bivalent booster increases frequencies of memory B-cells, recognizing shared and Omicron BA.1-specific epitopes.

To orient you to the slide, B-cells recognizing shared epitopes is shown on the left, and those to epitope specific to wildtype or Omicron BA.1 are shown on the right. Responses were assessed 7 days and one month after administration of the BA.1 booster dose. The data show a clear increase in mean frequencies of B cells, recognizing shared epitopes, and most importantly, in contrast to no change observed in wildtype-specific frequencies, the mean frequencies did increase for B-cells recognizing Omicron-specific epitopes.

In a separate analysis, we observed similar trends with a monovalent Omicron BA.1 booster. These data paired with the superior neutralizing response show that variant-adapted vaccines can expand relevant humeral immunity. Now, together with B-cell immunity, T-cell responses, as you heard earlier today, are also important in the control and clearance of SARS-CoV-2 infected cells and can provide immunity, particularly against severe COVID-19 outcomes. Though neutralizing titers may wane over time, improved stability in memory T-cell populations has also been reported.

Here we will show the first CD4 and CD8 T-cell analyses from our clinical study for the bivalent Omicron BA.4/5 variant-adapted vaccine booster as a fourth dose in individuals that received three prior doses of the original BNT162b2 vaccine. In a subset of participants, PBMC were collected before the booster dose and at 7 days, one month, and three months following the booster dose and evaluated by intracellular cytokine staining and flow cytometry using spiked

peptide pools, as illustrated at the bottom of the slide. I will show data describing the peak of the T-cell response, which occurs 7 to 28 days after boost.

Two distinct peptide pools were used to assess spike-specific T-cell responses, the first covering peptides in both wildtype and BA.4/5 spikes, and a second pool containing only peptides unique to BA.4/5, indicated to the right by the purple ticks spanning the stick diagram of the spike. On this slide, geometric mean frequencies as CD4 responses are shown on the left and CD8 responses, on the right, for individuals 18 to 55 years of age. These analyses show clear increases in both CD4 and CD8 responses in individuals who received the bivalent BA.4/5 booster. As indicated by the geometric mean fold rises following vaccination, shown below each figure, this increase was observed regardless of prior SARS-CoV-2 infection status. T-cell responses against BA.4/5 unique peptides were lower compared to the total spike-specific T-cell response given much fewer targeted epitopes but increased after booster administration, as well. And these findings are consistent with prior reports.

Now, having shown the immunological benefit of prior Omicron adapted vaccines, I'd like to turn your attention to our preclinical evaluation of vaccine candidates representing contemporary SARS-CoV-2 strains. Specifically, XBB-adapted vaccine candidates were evaluated as both a booster and primary series in BALB/c mice. We assessed the immunogenicity of the current bivalent BA.4/5 vaccine compared to XBB.1.5-adapted vaccines as either monovalent or bivalent formulations in combination with Omicron BA.4/5. The vaccines were administered as a fourth dose booster in mice that had received two doses of the original vaccine followed by one dose of the current bivalent Omicron BA.4/5 vaccine. Vaccine groups are shown along the x-axis, and pseudo virus neutralizing responses assessed one-month post-boost are indicated by the bars. Focusing on the colored bars indicating the current

predominant or emerging XBB strains, a monovalent XBB.1.5 booster elicited the highest neutralizing titers against each of the XBB sublineages, including 1.16 and 2.3, and the greatest relative increased response compared to the current bivalent BA.4/5 vaccine.

In additional ongoing studies, we are also evaluating an XBB.1.16 adapted vaccine as a third or fourth dose booster in mice. Preliminary data in mice that previously received two doses of the original vaccine followed by a third dose booster with either monovalent XBB.1.16 or monovalent XBB.1.5 show neutralizing responses are generally similar between the two vaccines. In the study shown here, XBB.1.5 adapted vaccines were evaluated as a two dose primary series in naive mice. Similar to results of the booster study, we show here that a monovalent XBB.1.5-adapted vaccine generated the highest neutralizing titers against the matched or closely matched XBB.1.5, 1.16 and XBB.2.3 strains, shown by the green, blue, and purple bars, respectively, when administered as a primary series. As SARS-CoV-2 seroprevalence predominates the adult population, these primary series data are most relevant for anticipated responses in the pediatric population without any prior SARS-CoV-2 infection.

Now before concluding the presentation, we would like to share our plans for supply of the 2023-24 formula, both in timing and vaccine presentation. Based on anticipation that a fall campaign would begin in August, and subject to regulatory approval, monovalent XBB formulations would be available. If a completely different formulation is chosen, this would follow the timeline from strain selection to vaccine availability of approximately 100 days, moving the vaccine availability to October. The proposed timing of supply in August aims to better align with the timing of the influenza vaccination campaign, where the majority of doses are distributed already by the end of September in the US. This approach could help to maximize vaccine uptake and protection against COVID-19 for the fall/winter season. Finally, this fall we

will also be transitioning to a single dose unit as the primary presentation, which should also support improved access and ease of administration.

In conclusion, the collective preclinical and clinical data shown today support a monovalent XBB containing vaccine for the 2023-24 formula based on three key findings. First, the XBB cluster of Omicron sublineages continues to dominate the variant landscape, improved humeral and cell mediated immunity that aim to protect against the spectrum of COVID-19 outcomes, and finally, preclinical data supporting that an optimal immune response can be achieved with the antigenically similar monovalent XBB-adapted vaccines based on XBB.1.5 or 1.16. And the current sera epidemiology together with collective real world evidence support a single dose for those five years of age and older, regardless of vaccination status.

I and my Pfizer and BioNTech colleagues would like to thank all of the participants in our clinical studies and their families, the sites and investigators, our CROs and partners, and especially the FDA and the committee. Thank you for your time today, my colleagues and I would be happy to answer any questions.

Q & A

Dr. Monto: Thank you, and thanks again to you all for keeping us on schedule. I just want to point out to the committee that the manufacturers will be available for further questions when we get to our general discussion later on. So, a few minutes now for specific questions. Dr. Gellin?

Dr. Gellin: Yeah, thanks for both of these. And I'll ask you, but I'll be interested in Moderna, as well. So is what you make for the US what you will supply to the rest of the world, or are you able to make different things for different markets?

Dr. Swanson: So we have been having ongoing discussions in informal exchange of the data that you've seen here with different regulatory agencies to help understand what needs to be

provided for the upcoming seasons. So I think that's an ongoing process. And we would be prepared to provide the vaccine for the selected formula. But I would go back to say, you've seen the overall variant epidemiology. It's very XBB driven within a set of XBBs that are antigenically similar. So I think we are narrowed down to a more limited options of what we're considering for the selection of the vaccine.

Dr. Monto: Thank you. And seeing no other hands raised —

Dr. McInnes: No, no, no. I raised my hand.

Dr. Monto: Pamela.

Dr. McInnes: Hi. Thank you, Arnold.

Dr. Monto: I'm sorry, now I see, now you've raised your hand.

Dr. McInnes: No, no, no. I raised it twice before. I don’t know what happened, but thank you.

Dr. Monto: I don’t know if that was the first.

Dr. McInnes: Yeah, well, we don’t know.

Dr. Monto: My apologies.

Dr. McInnes: So, I have a question for Pfizer. Yeah. So you have availability, and you will move to October, but I just think we're moving into a different kind of framework of thinking about timing. So you spoke about single dose unit, fall campaign, the monovalent would be off what was called back. This seems to me very much going back to the flu model, and that we get a one-time call, and then we all like march in, and we've been manufacturing at risk, and you know, maybe we're right, maybe we're wrong. But it seems like we should just have a different way of thinking about this, because if the periodicity of this is so much shorter than we think about flu, which I think it is, then we should stop talking about the 2023-2024 year, because maybe there is no such thing. Maybe it's a much shorter period of time that we're looking at for when this virus

changes and where this lineage, we have a new lineage, and we have to manufacture. So I guess we're sort of being pushed into thinking about it like, but it's not comfortable for me. So because of the rate. So can you answer that?

Dr. Monto: Well, maybe it will be. Maybe it will be going forward.

Dr. McInnes: Sorry?

Dr. Monto: Maybe it will be going forward. Right now we're limited to the situation that we find ourselves in.

Dr. McInnes: Yeah. But I don't want to think about it like that. Because it, like blocks me in from all sides. And it seems to me like this change in this virus is much more frequent.

Dr. Monto: I'm going to rule this, Pamela, I'm going, this is a very general discussion question.

Dr. McInnes: Okay.

Dr. Monto: And I think we can bring this up and talk about it this afternoon when we get back to a more general discussion where a lot of people can have a say.

Dr. McInnes: Can Pfizer respond to this in the meantime?

Dr. Monto: Well, very briefly.

Dr. Swanson: I will be very brief, and I think Kanta spoke to this very well this morning. And the surveillance of SARS-CoV-2 is truly a continuous process. You know, we don't, we can't predict what will be the true next steps of the virus. But we are seeing enough antigenic drift with the XBBs that it would warrant an update to the vaccine to optimize protection. But again, it will continue to be an ongoing process and not one time of year.

Dr. McInnes: Thank you.

Dr. Swanson: But I think that will be discussed this afternoon.

Dr. McInnes: Thank you, Arnold.

Dr. Monto: Thank you. Let's move on to Novavax. Dr. Filip Dubovsky will speak to us about their plans for the 2023-2024, as is now written, vaccine season.

Novavax Presentation — Novavax Data in Support of 2023-2024 Vaccine Update

Dr. Dubovsky: Thank you. My name is Philip Dubovsky, and I'm the president of Research and Development at Novavax. Today, I'll review our data on emerging variants and provide our suggestion for the vaccine composition for the ’23-‘24 season. Here's an overview of what I plan to cover. I will review clinical data that we previously shared with this committee showing that neutralizing immune responses generated by currently authorized vaccines drop off significantly for the XBB subvariants, thereby justifying a vaccine composition update. And I'll share some non-clinical primary vaccination data for XBB.1.5 and XBB.1.16 that shows both vaccines induce cross-neutralizing immune responses and that monovalent vaccines generate antibody levels of greater magnitude compared to bivalent vaccines.

When we boost previously primed animals with XBB.1.5 or 1.16, the vaccines induced cross neutralizing responses of comparable magnitude, and as discussed earlier today by the CDC and WHO, XBB.2.3 is becoming more prevalent in some parts of the world. The sequence is very similar to 1.5, and the receptor inhibition responses induced by XBB.1.5. Vaccines are similar for 1.5, 1.16 and 2.3. And as far as cellular responses are concerned, vaccinating with XBB.1.5 induces a polyfunctional Th1 biased CD4 response that's comparable for XBB.1.5 and 1.16. Conservation of these responses is expected, and it's been demonstrated for a variety of vaccine platforms. So taken together, we believe this data supports the selection of a monovalent XBB.1.5 strain for the ’23-‘24 Northern Hemisphere season, which is consistent with the recommendations from other global regulatory agencies and the World Health Organization.

But before I show you our data, I'm going to review our adjuvanted protein-based platform, as distinct from the other platforms discussed in this meeting. Novavax vaccine includes a full-length recombinant spike protein, shown here in red, that's presented in its native chimeric confirmation. The antigens form particles around a polysorbate core, shown here in blue, which improves antigen uptake and processing. We manufacture the antigen in insect cells, which have truncated glycans, and we hypothesize this improves epitope exposure to the immune system. And finally, the 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 resulted in high levels of efficacy in our initial phase three studies against prototype strain as well as against variants that circulated during our initial phase three studies.

So let's look at some clinical data that indicate the immune responses have dropped off for the XBB subvariants. This slide includes prototype and XBB.1 neutralizing responses for individuals who are vaccinated with our vaccine using a variety of different dosing regimens. These assays were conducted at the Dr. David Hill lab at Columbia University and can be compared to responses from different vaccines from his previous publications.

First, I'll display anti-prototype neutralizing responses derived from Novavax studies. I'm showing the neutralizing responses in individuals who received three doses of prototype mRNA vaccine and were boosted with our vaccine, in dark blue, compared to participants who received four or three doses of Novavax vaccine. Consistent with what has been previously described, homologous regimens have numerically higher responses. However, due to the small number of participants, precision of these estimates is relatively low. Added now in speckled pattern are results from previously published from Dr. 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 and

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. All these regimens provide high levels of neutralizing responses.

So now let's look at XBB.1 neutralization responses. Here you can see that for XBB.1, the responses are significantly lower, but similar, across the different dosing regimens irrespective of whether the primary series was mRNA or recombinant protein. And irrespective of whether the boost was protein, recombinant protein, prototype, or bivalent mRNA vaccine, the responses were reduced compared to the prototype neutralizing responses displayed on the left. These findings are consistent with the structure function data previously shared with this committee that demonstrate important neutralizing sequences that existed in a prototype strain, the blue BA.5 variant, are not present in XBB subvariants. From this data, we infer that all vaccine regimens tested are performing comparably against the currently circulating XBB subvariants, and all vaccines will benefit from updating to contemporary strain to optimize neutralizing immune responses.

Okay, let's look at some immunization data in mice for XBB subvariants. I'll start with primary immunization data where mice received two doses of vaccine without a boost. Displayed here are neutralization responses against a number of variants after primary vaccination with prototype, XBB.1.5, and XBB.1.16 vaccine. I've annotated the currently circulating XBB subvariants in yellow. The prototype strains are displayed on the left-hand side of the slide, and similar to what we saw in the clinical data, their responses are good against prototype, but very low against both XBB subvariants. The middle panel displays responses after vaccination of two doses of XBB.1.5, and the neutralizing responses are similar for XBB.1.5 and 1.16. And the same is true for mice vaccinated, on the right-hand panel, with two doses of XBB.1.16 vaccine.

The responses for 1.5 and 1.16 are comparable. As expected for primary vaccination, homologous responses are slightly higher than heterologous responses for both subvariant vaccines. The conference intervals are broadly overlapping.

Okay, now let's look at some responses after monovalent and bivalent vaccination. This slide shows neutralizing responses after primary vaccination with two doses of monovalent XBB.1.5, on the left-hand panel, and two doses of bivalent vaccine containing prototype and XBB.1.5, on the right-hand panel. As we saw in the previous experiment, vaccination with a full dose of XBB.1.5 induces comparable neutralizing responses to XBB.1.5 and 1.16. However, on the right-hand panel, vaccinating with the bivalent vaccine that contains half the XBB.1.5 antigen load induces lower responses to both XBB subvariants. Numerically, the response is more than 50% lower. So from these data, we conclude that vaccinating with either XBB.1.5 or 1.16 induces cross-neutralizing responses. This is not surprising because the variant spikes are structurally very similar. And we also see indication that a monovalent vaccine may be advantageous compared to bivalent vaccine.

So now let's look at some boosting data with XBB subvariants. We have boosting data in primed mice as well as in primed versus macaques. Boosted responses are important because in general, the US population is well primed with multiple rounds of vaccination and serial infections. The responses seen in these animal models may be more relevant than the primary vaccination data we just reviewed. On this slide, we're showing primary vaccination and boosted neutralizing responses in mice. All animals were primed with the bivalent vaccine containing prototype and BA.5. The results after the two-dose priming series are displayed on the left-hand panel. The bivalent vaccine induced good responses to both prototype and BA.5 but very low

responses to the XBB subvariants. These lower responses to antigens included in currently available vaccines is similar to what we saw in our clinical data.

The middle panel shows responses after these primed animals were boosted with XBB.1.5. XBB.1.5 is a very good immunogen, and responses to both XBB.1.5 and 1.16 increased more than 35-fold from before boosting and are comparable in magnitude to each other. The levels achieved after boosting with a single dose of XBB.1.5 are also comparable to the levels achieved for both prototype and BA.5 after a full two dose priming series, on the left. The same is true in boosting with XBB.1.16, on the right-hand panel. We see no specific benefit for boosting with XBB.1.16 in this experiment. S

o a common way to visualize the differences in immune responses is through antigenic cartography, as was described earlier. Displayed here is the antigenic cartography of neutralizing responses in mice. In this two-dimensional display, e square represents a twofold change in immune response. So one square is a twofold difference. Two squares is fourfold, and so on. On the left-hand side, you can see that after priming with two doses of bivalent vaccine containing prototype and BA.5, the antigenic distance is very broad. This is comparing prototype, in green, to XBB.1.5, in yellow, and separately, comparing prototype, in green, to XBB.1.16, in blue. Annotated below the graphic, you can see the antigenic distance from prototype to both XBB subvariants is greater than 30-fold following primary vaccination with bivalent vaccine.

This antigenic distance isn't surprising, because as we have previously discussed with this committee, the neutralizing sequences present on prototype and BA.5 are largely not present in the XBB subvariants. The middle panel shows that after boosting with XBB.1.5, the antigenic distance narrows, and XBB.1.5 provides good neutralization to XBB.1.16. This is a different analysis from the prior panel and compares the antigenic distance between XBB.1.5, in yellow,

and 1.16, in blue. The antigenic distance is less than one, which is considered a matched response. On the right-hand panel, the same is true in boosting with XBB.1.16. The vaccine induces good cross neutralization responses to one five and once again the antigenic distance between 1.16, in blue, and XBB.1.5, in yellow, is less than one.

Okay, let me show you some additional boosting data in non-human primates. In this experiment, we primed groups of five recess macaques with two doses of prototype, on the left, two doses of BA.5, in the middle, or two doses of a bivalent containing prototype plus BA.5, on the right-hand panel. Eight months later, they were boosted with XBB.1.5, and when you compare the XBB.1.5 and 1.16 responses in each priming regimen, you can see they're comparable. So for the prototype primed animals displayed on the left-hand side, XBB.1.5 and 1.16 responses are similar. In the middle panel, for BA.5 primed animals, XBB.1.5 and 1.16 responses are similar. And the same is true for animals primed with bivalent vaccine on the right-hand side. The magnitude of the XBB subvariant responses was greatest when primed with monovalent BA.5 and lowest when primed with prototype alone. This makes sense, because we know that XBB is more closely related to BA.5 than it is to the prototype. So from this data, we conclude that when used as a booster, XBB.1.5 induces comparable neutralizing responses to XBB.1.5 and 1.16.

Now let's look at some data from XBB 2.3, which, as we've heard, is emerging in some countries. This slide displays the sequence differences between XBB.1.5, 1.16, and 2.3. On the left-hand side of the triangle, as we've heard earlier, you can see that XBB.1.5 and 1.16 differ by two amino acids, only one of which is in the receptor binding domain. And we indicated this with the asterisks. On the right-hand side of the triangle, XBB.1.5 differs from 2.3 spike by three

amino acid residues, once again, only a single change in receptor binding domain. Therefore, you would predict the immune responses induced by 1.5 would be relevant for both 1.16 and 2.3.

Additionally, you can see in the bottom of the triangle there's greater sequence divergence between XBB.1.16 and 2.3 with a total of five amino acids differences in two changes in the receptor binding domain. This suggests that XBB.1.5 may be the best option to include in the vaccine because there's less divergence from the other two emerging XBB subvariants. Selecting XBB.1.5 hedges our bet, because it is unknown if subsequent variants will arise for 1.5, 1.16, or 2.3, or perhaps all three. Neutralizing data for XBB.2.3 was not available when these slides were submitted. However, we do have human ACE2 receptor inhibition data, which is considered a functional immunoassay, and I'll describe this in the next slide.

So ACE2 receptor inhibition assays measure the ability of antibody that has been generated by a vaccine to block the interaction between the variant spike protein and the human ACE2 receptor. This interaction is required for viral entry into human cells, so functionally, it measures the same biological pathway as a neutralizing assay. Displayed in this graph is data from last year's strain change study conducted in Australia that correlates our validated neutralizing the assay to our validated receptor binding inhibition assay. And the two assays are very tightly correlated, with a Pearson's correlation coefficient of 0.96. This degree of correlation suggests that ACE2 receptor inhibition can be used as a functional surrogate for neutralization assays.

Okay, let's look at XBB.2.3 receptor binding inhibition data for mice and non-human primates. In this experiment, we primed mice with bivalent vaccine, which included prototype plus BA.5, and they were boosted with XBB.1.5, and the responses were evaluated in the receptor binding inhibition assay. You can see that functional responses were robust for all three

subvariants and nearly identical for 1.16 and 2.3. As we saw in the previous slide, XBB.1.16 and 2.3 differ from 1.5 by a single amino acid in the receptor binding domain, so preservation of receptor inhibition was expected. A couple of days ago, we received murine neutralization data which corroborates this receptor binding inhibition data. And in fact, in that dataset, XBB.1.5 boosted resulted in numerically higher 2.3 neutralization compared to animals that are boosted with XBB.1.16.

Now let's look at receptor binding inhibition in non-human primates. In this study, we primed groups of five resistant macaques with prototype, BA.5, or a bivalent containing prototype plus BA.5, and they were boosted eight months later with XBB.1.5. XBB.1.16 and 2.3 responses were similar, irrespective of which priming regime was used. On the left, when primed with prototype, the 1.16 and 2.3 responses were similar. In the middle, when primed with BA.5, 1.16 and 2.3 responses were similar. And the same is true when primed with bivalent vaccine, on the right-hand panel. From this data, we conclude that XBB.1.5 induces functional immune responses to XBB subvariants, including 2.3, and further supports of selection of XBB.1.5 for the ‘23 fall season.

So now let's briefly look at some cellular immune responses. We have intra-cytokine staining data for both animal models. Here we've displayed CD4 responses for mice that were either primed with two doses of prototype, on the left, or two doses of bivalent vaccine containing prototype plus BA.5, on the right, and both groups were boosted at one month with XBB.1.5. This data displays CD4 cells that were staying with interferon gamma, TNF, and IL-2 for Th1 cytokines, and IL-4 is a model Th2 cytokine. The cellular responses are generally maintained across all variants, and boosting with XBB.1.5 results in a comparable signal for 1.5 and 1.16.

So let's look at some cellular data from non-human primates. Here we've displayed the Th1 and Th2 CD4 responses in recess macaques who are primed with two doses of bivalent vaccine containing prototype plus BA.5 and boosted with XBB.1.5. Th1 responses to those for interferon gamma, IL-2, and TNF-alpha are shown on the left, and Th-2 responses, IL-5 and 13, are shown on the right. The Th1-biased cellular responses are maintained across variants, and we've observed a very similar response for XBB.1.5 and 1.16.

Okay, let's go to the last side, just summary. So based on the data we've gathered on the emerging variants, Novavax supports the monovalent XBB.1.5 strain for the ‘23-‘24 Northern Hemisphere season. This strain composition is consistent with the World Health Organization recommendations as well as other global regulatory agencies. We know from previous clinical work that immune responses have dropped off for currently circulating XBB variants. This observation is confirmed from murine and non-human primate data I’ve shared with you today.

I've shown you data that vaccinating with XBB.1.5 induces comparable neutralizing responses to XBB.1.5 and 1.16, and that a monovalent XBB.1.5 appears to be better than a bivalent. US population is well primed with serial infections and serial vaccination. So data that monovalent XBB.1.5 boosts well and induces comparable neutralizing responses to other XBB subvariants is relevant. And XBB.1.5 is antigenically similar to XBB.1.16 and, importantly, to XBB.2.3. And furthermore, XBB.1.5 induces antibodies that block XBB.2.3 from binding to the human H2 receptor. And finally, XBB.1.5 induces polyfunctional TH1-biased CD4 cellular response to the other XBB subvariants.

Our approach has been to manufacture the vaccine at risk, and we continue to manufacture XBB.1.5 at commercial scale. And we're filling this in single dose vials to support

US fall vaccination campaign. The selection of a strain other than XBB.1.5 will result in delay to our vaccine's availability. Thank you. I can now take your questions.

Q & A

Dr. Monto: Thank you, Dr. Dubovsky. Again, keeping us right on time. Questions? Dr. Levy.

Dr. Levy: Yes. Hi, Dr. Dubovsky. Thank you for that excellent presentation. You presented some data on cellular immune responses to the Novavax vaccine. Has Novavax considered looking also at CD8 cells, and do you view those as potentially relevant to host defense against Coronavirus? Thank you.

Dr. Dubovsky: Yes, certainly. Certainly there's data out there that a CD8 response may be relevant. Normally, as a protein-based, either adjuvant and protein-based, you wouldn't think a CD8 would be the strong suit of this platform. And we know from animal studies, we do, in fact, induce CD8 cells, and there's been some recent work from our collaborators at Scripps who also have described a CD8 response, but it's not as robust as you'd expect from other vaccine platforms.

Dr. Levy: Thank you.

Dr. Monto: Dr. Sawyer.

Dr. Sawyer: The last thing you mentioned was that a selection of a strain other than 1.5 would delay your production. Can you give us a, what is your window between time of selection and availability of vaccine?

Dr. Dubovsky: Sure. We, we've previously talked about, for a common protein vaccine like ours, it's much like the flu timeframes. So we need pretty much six months from when a strain is named to when we can have commercially available product. Now we have other candidates that

we've advanced through the manufacturing process. The next one would be 1.16. It'll be available approximately eight weeks after 1.5.

Dr. Sawyer: Thank you.

Dr. Monto: Dr. Berger.

Dr. Berger: Thanks. I was going to ask the same question, and I'll ask it and make it a slightly different way, then. You know, I'm just curious, because of the WHO said they were going to be meeting every six months to make determinations about whether or not to update the strain that should be included in a vaccine. I'm just curious if the FDA went to a similar model for having meetings every six months and doing strain selection at that speed, how would Novavax be able to manufacture or deliver on that type of a timeline?

Dr. Dubovsky: Yeah, so the pattern that we've followed and we're continuing to follow is that as new variants emerge, we make them. We make them at a lab scale. We test them in animals to look for cross-reactivity and antigenicity. And we moved them into the early stages of commercial manufacturer. So that's how we're able to deliver this vaccine on time because we'd, through our work, moved forward with it into commercial manufacture before this meeting even happened. And the same is going on in real time. So we're making new variants as they emerged and look interesting to us.

Dr. Berger: Thank you.

Dr. Monto: Thank you. I see no other hands raised, and somehow, we are right on schedule. I want to thank the presenters and especially the committee members for their restraint in holding back and asking a lot of questions at this point. We'll have our chance this afternoon. So we now have a break, and we resume with the Oral Public Hearings at 1:00 Eastern.

Open Public Hearing

Dr. Paydar: Go ahead, Dr. Monto.

Dr. Monto: Welcome to the Open Public Hearing session. Please note that both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the advisory committee, 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 relationships that you may have with the sponsor, its product, and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of expenses in connection with your participation in this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial 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. Over to you, Sussan.

Dr. Paydar: Thank you, Dr. Monto. I would like to pass the meeting to Dr. Marks to make Open Public Hearing remarks. Dr. Marks.

Dr. Marks: Thanks very much. Thanks very much Sussan and Dr. Monto. Just wanted to start the Open Public Hearing by saying that we very much appreciate diverse viewpoints as part of the Open Public Hearings. I just want to make sure that the public who's listening know that those who make public remarks during the Open Public Hearing, those remarks are not necessarily endorsed by the Food and Drug Administration, nor do they represent our views. They are the views of those who are making those remarks. And we do ask that our speakers remain courteous and do not have direct attacks at committee members or individuals when they make their remarks. So thanks very much.

Dr. Paydar: Great. Thank you, Dr. Marks and Dr. Monto. Before I begin calling the registered Open Public Hearing speakers, I would like to thank all OPH participants on behalf of the FDA and the committee for their interest in participating in today's VRBPAC meeting and sharing their views and comments. FDA encourages participation from all public stakeholders in its decision-making processes. Every advisory committee meeting includes an Open Public Hearing session during which interested persons may present relevant information or views.

I would also like to add the following guidance that the 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. With that guidance, I would like to begin. Every speaker will have four minutes to make their remarks. Let's begin with our first OPH speaker, Ms. Melissa Miller. Ms. Miller.

Ms. Miller: Good afternoon. My name is Melissa Miller, and I have no financial or other conflicts of interest. Next, please. What we know now, it's unwise to vaccinate during a pandemic, as it encourages rapid viral evolution, and FDA is already working to pick the strains for yet another vaccine? Covid mutations are too rapid for technology to keep pace with changes and be effective. Therefore, vaccine is not preventive. Any vaccine that does not prevent transmission, infection, and disease, only hospitalization, is a medical treatment and not a vaccine. Next, please. Other countries fully stopped COVID-19 vaccines, and some countries never went after kids, unlike the US. Next, please.

Disability has been increasing since May 2021, a three to four Sigma event, year on year. What is causing this? Next, please. As evidenced in the Mayo Clinic research, a number of doses

of vaccinations given, the more you vaccinate, the more infections one has. The yellow line is over three doses. What do you think happens next? Next slide, please. The US is the only country in the world targeting children as young as six months old with COVID-19 vaccines, which are still under EUA. My question is, who is profiting at the expense of the children's health? Next, please.

Recent MMWR article showed half of children had systemic reactions after a third dose. This is just a small number of children who have received the third dose. Next, please. Based on the slide that CDC's Ruth Link-Gelles presented, parents have wisened up. So 91.1% of children under 2, 89.1% of children under 4, and 60% of children under 11 remain unvaccinated. Next, please. When chronically under-reported VAERS system is showing the numbers below, you have to realize something is off and course correct. Next, please.

Here are my recommendations: Stop trying to get ahead of Covid. It's here to stay just like influenza and influenza-like illnesses. There are successful treatments and prevention. No, not Remdesivir or Paxlovid, the last one which was only tested on unvaccinated people. Treatment of secondary pneumonia with antibiotics is what's needed, not vents. Thank you.

Dr. Paydar: Great. Thank you, Ms. Miller, for sharing your views. Next is Mr. Kermit Kubitz.

Mr. Kubitz: Do you have my slides? Yes. I will address three topics in future Covid vaccine development. First, reasons for a monovalent XBB vaccine. Second, need for expedited FDA BLA vaccine approval process. And, C, lower cost vaccine approaches. Next slide. Reasons for a monovalent vaccine. First, the XBB.1 lineage is the dominant strain circulating now. Second, using a monovalent vaccine will maximize immunity response production. Preclinical data on XBB.1 candidate vaccines shows higher neutralizing antibody response. Third, prior variants are

not circulating as much. Fourth, as a contingency backstop for new variants, an expedited BLA process, as discussed below, should be developed by the FDA. See slide three. Next, slide.

Given extensive vaccine experience now, BLA approval process should be expedited using these criteria. First, well understood vaccine manufacturing technology like mRNA from Pfizer and Moderna or Novavax and other global vaccines like Corbevax inactivated virus vaccine widely used in India and Indonesia are well understood now. With good manufacturing process methods and, if necessary, rapid small cohort testing for safety, 1,000 to 3,000 persons, an expedited vaccine approval process could be undertaken. Next slide.

Low-cost vaccine approaches should be adopted. Removal of government subsidies necessitates lower cost than Moderna and Pfizer mRNA vaccines. Simpler vaccine approaches, such as an inactivated virus with an adjuvant booster like Corbevax, developed by Dr. Peter Hotez and widely used in India and Indonesia for lower cost vaccine distribution, and they also do not require low temperature storage. Such simpler vaccines are already in widespread use, and a simpler inactivated virus vaccine with an adjuvant booster could be deployed faster and more cheaply in the event of or need for sudden new vaccine in response to new variants.

Finally, I think we should expedite the process of developing a pan coronavirus vaccine. The work by Dr. Saunders (phonetic) and Haynes (phonetic) at the Duke Human Vaccine Institute, instead of targeting the entire spike protein could generate antibodies by targeting the receptor binding domain. And the funding for such a pan coronavirus vaccine should be expedited. Thank you very much for the opportunity to speak. I was vaccinated. I had a breakthrough infection. But, due to the vaccine, it was mild, and I only had a headache and a temperature for three days. Thank you, Dr. Monto, Dr. Marks, Dr. Kaslow, Dr. Link-Gelles, Thornburg and the staff of the FDA. Thank you very much. Bye.

Dr. Paydar: Thank you, Mr. Kubitz, appreciate your presentation. Next is Dr. Mary Elizabeth Christian.

Dr. Christian: Good afternoon. Thank you for the opportunity to speak to the committee. I have no conflicts to disclose. I'm Mary Elizabeth Christian. I live in Baton Rouge, Louisiana. I'm a breast surgeon who's no longer practicing due to a disabling genetic condition, but I'm also a mama, a yaya, and an advocate. I was a daughter until August of 2021 when my parents died. My parents were vaccinated in January of 2021. They believed they were safe, and so they went out to lunch for their 62nd anniversary on July 18th. Three days later, they had Covid. And three weeks later, they were both dead from Covid. They were buried together at the Louisiana National Cemetery with only this grave-side service. A week later, on August 18th, boosters were approved. I still must wonder, if they had been able to be boosted before they were infected, will one or both of them be alive today? Next slide.

My daughter was pregnant when the first vaccine became available. There were limited data for use in pregnancy. But, after careful consideration, she was vaccinated. She said to me at the time, I want my son to know I did the right thing. We subsequently traveled hours to enroll her infant son in a vaccine trial, though he was disqualified due to his low birth weight and prematurity. He was vaccinated on the first day it was offered by his local health department in Omaha.

Booster approval for children, in particularly the under-fives, came only after many worry filled months. By then, vaccine administration infrastructure had collapsed. We spent many hours online, on the phone, and searching parent-created spreadsheets for location. Despite living in cities with dedicated children's hospitals and with connections to our local community, through my practice and her internship, we could not locate a site within driving distance of

Omaha or Baton Rouge for almost two months. I can only imagine the difficulty faced by families with additional barriers such as transportation or economic barriers.

Our family includes many high-risk individuals. We have family members who are immune compromised, an adult daughter with level three autism and mitochondrial disease, we have our grandson, his one-month old preemie sister, a previously healthy husband who now has post Covid hypertension, and my octogenarian in-laws. We are not unique. Many families include cancer patients, elders, immune compromised, or those with comorbidities. Those families include my former breast cancer patients who, though cured from breast cancer, now must face the risk of Covid infection.

We all must now venture into a community, which has largely abandoned masking and air quality measures. Even our excess of healthcare poses substantial risk, as they too have abandoned both air quality and masking. In Omaha, the public schools start in two months. If vaccines are not approved quickly, teachers, staff, and students will return without booster protection or vaccine protection. Children of staff and students' younger siblings will be in the daycare where my grandchildren go. Teachers, staff, and children will go home to their families who may also be at risk. They need the opportunity to protect themselves and others. Next slide.

I can wear a mask, and I can carry my mini-CR box, but I cannot move vaccines into the community. You are tasked with evaluating the excellent science discussed this morning, and I appreciate your work in that regard. We all live in communities with the medically vulnerable. Sequential approval means even the most high-risk group must venture into communities which now have waning immunity and a lack of layered protections. Additionally, those who are all willing to be vaccinated may simply give up before finding a site for their family, or they may be unable to take off multiple days from work for vaccines to be administered on different

schedules. Consider what it might do to update if everyone from yaya to the baby could get vaccinated on the same day. Next slide. I urge you to approve updated vaccines for all age groups. Urgency and timing matter. It might have saved my parents, and it may well save my daughters and my grandchildren. Thank you.

Dr. Paydar: Mary, thank you so very much for sharing your personal story with us. I'm so sorry to hear about your difficulty, loss of parents, and all the other difficulties you've had to endure as a family. Thank you so much for taking time to be here with us today. Next is Dr. David Wiseman.

Dr. Wiseman: Thank you. Please see our written remarks. I have no conflicts. Next. FDA's brief echoes recent international statements acknowledging natural immunity, rapid waning, and imprinting. Next. The death rate is low, despite 17% vax uptake. Do people agree with Dr. Offit that chasing variants is a losing game? Next. Mistrust blights other vaccines. Why? Next. Perhaps they don't work as represented. They are gene therapies. Safety signals are ignored. Next. Rather than a safe and effective standard under EUA, they may be effective. Next.

CDC showed waning to zero at three months the negative VE, suggesting immunocompromise. Next. And consistently by age, below FDA's 50% target, going negative. Next. Three months after your introduction, XBB alarmingly evaded bivalence in studies omitted from FDA's January brief. Next. Along with Cleveland Clinic, noting that they were not alone in finding a possible association with more vax doses and higher risk of Covid, they pre-printed this week that Covid risk is lower in out-of-date than up-to-date adults. Next. Does FDA's brief suggest vaccination drives variants? Next. Excluding these gene therapies from guidance does not change biology or safety concerns. Next. Where is FDA's gene therapy group? Why did makers think their vaxxes were gene therapies?

Next. We respectfully disagree with Dr. Marks. Next. The National Cancer Institute shows reverse transcription is possible. Next. NIH show message and spike enter the nucleus. Next. Episomal transmission does not need integration. Next. Regulators exceed to BioNTech. Next. Waiving carcinogenicity studies or on gossamer grounds. Next. FDA scientists say DNA can be oncogenic. Next. Kevin McKernan's coming report of possibly replication competent residual plasmid template DNA with antibiotic resistance and undisclosed SV40 promoter sequences suggests adulteration. Next.

With minimal comparability testing, Pfizer switched processes for clinical and commercial use. Next. Hardly meeting the same process criteria, justifying abbreviated testing for variant vaccines. Next. Pfizer's tris changed effective translation and likely safety and efficacy. Same process? Next. The bivalent process change yielded novel heterotrimers with untested toxicology and likely misbranding. Next. VAERS cancer reports are alarming. Next, CDC finds cancer signals. Next. They said they couldn't find stroke signals outside of VSD. But, next, look in CDC's recent FOIA disclosure. Next. Our normalized ratios yielded alarming signals. Next. Temporal associations between vax coverage and all-cause mortality persist.

Next. Dr. Portnoy's questions last year about spike production was dismissed as academic with no FDA insistence for these studies. Next. Lipid nanoparticles widely distribute. Next. Spikes persist for up to four months, next, an mRNA for up to 28 days. If you can't say where and for how long these gene therapies induce spike production, don't ask people to vax. Next. Is this even a good idea? Dr. Fauci writes, vaccines have never effectively controlled these sorts of viruses and are not expected to do so. Next. Dr. Marks questions incrementally modifying variant specific vaccines. Next. Pfizer's boast of flying a plane under construction erodes public trust.

Next. There's no pandemic anymore. Regulate these products as gene therapies. No free passes to poorly understood platforms. Consider the cumulative toxicity of these products. Chase safety, not variants. Help the vax injured. Restore public health. And thank you for listening, and thank you, Dr. Paydar, and your team for an excellent job that you do. Thank you.

Dr. Paydar: Thank you, Dr. Wiseman, for sharing that PowerPoint with us. Appreciate it. Next is Mr. Don Ford. Mr. Ford.

Mr. Ford: Hello. My name is Don Ford, and I have no conflict of interest. Next slide. Next slide. The main points of this presentation are approving a monovalent based on XBB.1.5, approving Novavax, regardless of previous RNA, approving a new primary series to overcome imprinting, and study Novavax as a treatment for long Covid, also altering recruitment criteria for Novavax clinical trials for pediatric vaccines. Next slide. The WHO and the EU both recommend a monovalent based on XBB.1.5. If we go higher, we run into the BA.1, BA.2, BA.5 debacle with XBB being a BA.2 subvariant recombinant, leaving the public without a targeted vaccine. Next slide.

The bivalent has been shown to dilute the antigen, weakening the response while suffering from imprinting. The concern is that this will limit vaccine effectiveness and booster uptake. Next slide. Americans are being punished for following the guidance to get RNA first. No data supports that it is unsafe to switch from RNA to Novavax. Many countries already allow people to switch. Gatekeeping Novavax is damaging the perception of public health in America. Next slide. Israel has allowed Novavax access since mid-September of last year, and that includes a new primary series of desire. Next slide.

New alarming data has come to light. Covid can cause brain cells to fuse. Next slide. Novavax reduces nasal viral replication, which protects our brains. Unfortunately, RNA only

offers limited protection in this capacity. Next slide. In a balanced cohort, Novavax was shown to be twice as protective from hospitalization when compared to an equal body of patients who received RNA. Next slide. Internal FDA CDC data shows that RNA only offers protection from hospitalization for 110 to 170 days. This is not sufficient for a virus that can fuse brain cells. RNA once a year is not satisfactory to protect the American people. Next slide. RNA only achieves its best reaction if there are gaps between shots. The gap needed is greater than the window of protection. This leaves Americans vulnerable to hospitalization. Next slide. Novavax can be taken successively to maintain protection with no gaps. This provides consistent protection. Response continues to increase beyond anything RNA has achieved. Next slide.

In contrast to RNA, it has been demonstrated that Novavax protection from hospitalization has no clear endpoint existing beyond testing windows. That means no gaps. Next slide. Novavax was a product of operation warp speed paid for by US tax dollars, yet Americans have extremely limited access to the product they funded. Next slide. The US is one of only a few countries using draconian restrictions for Novavax.

Approval is required for greater access to Novavax, including a new primary series of at least four months since previous Covid vaccine. Next slide. It has been demonstrated that a new primary series is required to overcome imprinting. Not doing this could leave the vaccinated vulnerable to hospitalization, further damaging the public's perception of vaccine effectiveness and public health. Next slide. It has been demonstrated that people who get Novavax see relief from long Covid symptoms. We require studies from the NIH and Novavax from the anecdotal reports showing recovery post vaccination. Next slide. There are many examples, but far too many to mention here. Next slide.

Novavax is designed to target conserved epitopes that are common among all variants, including mutated persistent virus. That means it likely assists the immune system in finding and targeting persistent virus, which is a primary driver of long Covid. Next slide. Changes are needed to the trial recruitment for Novavax to bring a pediatric vaccine to market, specifically requirements that cohorts be infection or vaccine naive. This is not the population we will be vaccinating and will delay protecting children. Next slide.

Funding needs to be allocated from Project NextGen to expedite production of Novavax's pediatric vaccine. Spending caps created during the debt ceiling will limit Congress's ability to create investments in treatments and vaccines for at least two years. We cannot wait that long to protect our children from fused brain cells. Next slide. Restriction on Novavax creates a vaccine equity issue. This prevents Americans from being protected from Covid. It is cruel to limit the tools at hand. Demand exists, but the current recommendations artificially limit access. Next slide. Next slide. The next vaccine should be a monovalent targeting XBB.1.5 or allow manufacturer discretion. To avoid imprinting, allow Americans to get a variation of a primary series of Novavax when we change variants. Allocate NextGen funding and reassess trial recruitment criteria to expedite Novavax bringing a pediatric vaccine to market. Remove the regulations that will limit Novavax access. Limiting Novavax access is a vaccine equity issue that we need to fix. Thank you for your time.

Dr. Paydar: Great. Thank you, Mr. Ford, for your presentation. Next is Mr. Kevin McKernan.

Mr. McKernan: Thank you. I have no conflicts to disclose. I have 25 years of experience in the genomic space. I've worked as a team leader of R&D at the Human Genome Project at Whitehead MIT, and I have over 57,000 citations to publications in my space and multiple patents on PCR and sequencing. Next slide, please. No conflicts. Next slide. In February, I used

mRNA vaccines as a spike in control for some RNA sequencing libraries and, to my shock, discovered that the expression vectors for the vaccines are still in the vials. I looked at this in over a dozen vials, and it appears that this expression vector is above the EMA guidelines in the FDA guidelines. You can see this in this pre-print that's described here. Next slide.

As a refresher, there's two different processes that have been discussed in this BMJ article. The clinical trials were run in process one, which uses in-vitro transcription off of synthetic DNA, but they switched to process two for a scaleup, which used e-coli to amplify plasmids and those plasmids are what still remain in the vials and we're not within the clinical trial. Next slide. This is another depiction of this process. You can see getting plasmids out of these e-coli is a challenge and can sometimes leave to residual plasmids inside the vaccines. Next slide. These are the expression vectors that we discovered on the left in the Pfizer vaccines. They also exist in the Moderna vaccines, but they're a little bit different. The Pfizer vaccines specifically have this SV40 promoter, which was not disclosed in the expression vector map that was given to the FDA or, I'm sorry, the EMA, but the expression vector has a 344 base per promoter with a nuclear localization signal known as this SV40 promoter. Next slide.

So we went to verify this by designing quantitative PCR assays that target the spike sequence and the vector sequence. Next slide. And this work demonstrated that with even one to a hundred dilutions, you could get CTs of 22 for the DNA that's in these vials for the vector, which is not part of what should be in these vials. We did this in triplicate across eight vials. It's very consistent, and they are over the EMA and the FDA's limits. Next slide. The EMA has a ratio metric limit that looks at RNA to DNA ratios, and you can measure, you should expect an 11.5 CT offset between the spike and between the vector. What we see is only five to seven CT

difference, which means there's an 18 to 70-fold over the limit of the 330 nanogram per milligram recommended by the EMA. Next slide.

You can readily assay this in any other lab around the world now. If you put these vaccines directly into quantitative PCR, you can get CTs as low as 17. This is very important to know because Covid was diagnosed with CTs less than 40, which is over a million-fold higher contamination being injected than what you might get from a nasal swab. Next slide. These vials were sent to us anonymously in the mail, so we do not have the cold chain. However, we can measure the RNA integrity by putting them on electrophoresis systems, and we do not see a substantial difference in the RNA integrity from the vials that we received versus what's been published about these in the past. Next slide.

Various people on Twitter have now begun to reproduce this. In addition, I'd point to the EMA's documentation where they have an 815-fold variance across 10 lots of double stranded DNA contamination documented in the EMA process. Next slide. There are some risks to this. Double stranded DNA can create interferon responses, and Keith Peden at the FDA has done great work demonstrating the risks of DNA integration into the genome if these things are in vaccines. Next slide.

The call to action here is all of these primer sequences are now public, and people are downloading them and trying to reproduce this work. You can reproduce this work in 60 minutes with a microliter of the vaccine, which is 1/300th of a dose, for less than $10. I encourage everyone to try and do this to understand what we have at foot. I will note we did not measure any of the bad lots that are in the Schmeling et. al paper that demonstrated high adverse events in certain lots. We were measuring what seemed to be normal lots. Next slide. Thank you for your time and consideration.

Dr. Paydar: Great. Thank you so much, Mr. McKernan, for your presentation. Next is Mr. Joaquin Beltran. Joaquin.

Mr. Beltran: Thank you so much. Full transparency. I was a Biden-Harris 2020 regional director, currently a small retail investor of Novavax, who supports vaccines ongoing availability, vaccinated with two Pfizer's, one Novavax, and never had Covid. Thank you so much for having me today. My name is Joaquin Beltran, and today I am urging the FDA to, one, approve Novavax's updated XBB booster; two, update booster guidelines for equal access regardless of booster history; and, three, expand Novavax access to children under 12.

Next. As the public health emergency ends, it's clear we are now in a shadow pandemic with long Covid as its own pandemic, re-infections creating cumulative risk, hospital-acquired infections at an all-time high in some states, testing and data virtually gone, a need for improved air quality in buildings, healthcare services collapsing, mass transmission outpacing our pharmaceuticals, and economic hardship from all these ongoing challenges. Next. Although we are currently in a lull, we are at the second highest baseline during the last four springs, and the pattern suggests we will have a surge as soon as this summer. As we have reached an upwards estimate of 1.4 million excess deaths in less than 3.5 years, it is clear we have to act.

Next. We have to use every tool available to reduce transmission. Next. And that means we have to utilize a lifesaving tool that is the Novavax COVID-19 vaccine. Next. Recent data shows there is a drop of effectiveness against recent variants, making it clear we need to update vaccines. Next. Early data shows the XBB booster shows increased effectiveness against recent circulating variants. Next. Safety data remains high with a recent study showing decreased reactogenicity upon a fourth dose of Novavax. Next. Recombinant vaccines have a history of

high safety profiles like flu cell vaxes flu vaccine, which uses the same vaccine dose for everyone six months and up. Next.

We also need to urgently update the booster guidelines for equal access to boosters, regardless of prior booster history. In particular, language in the current guidelines has prevented many from obtaining this lifesaving vaccine. This language is the following, quote, but have not previously received a COVID-19 booster, and if they cannot or will not receive mRNA vaccines, end quote. Pharmacies across the country have cited this language as preventing them from giving Novavax to those with prior mRNA boosters. There are some examples. You can go to social media and look up Novavax, and you'll find countless stories of people being denied Novavax with people in some cases having to lie, next, or having to go to another state or country to get this lifesaving vaccine. Next. Next. One person shared about the challenge of obtaining this lifesaving vaccine that was paid for by taxpayer dollars. Quote, it’s brutal trying to protect yourself in a DIY pandemic. Next. There's no scientific reason for denying boosters of Novavax. Next. Next.

Lastly, we need to expand Novavax to children under 12, as Covid poses a threat to children's lives and their risk of long Covid. Next. And we need to reduce spread. A recent study shows that 70% of transmission in households were from a pediatric index case. Next. Two studies, one in JAMA, one by the CDC, shows elevated risk of Type 1 diabetes for children who had Covid, showing that children remain vulnerable and need further protection. Next. I’m urging the FDA to approve Novavax’s updated XBB booster, update booster guidelines, and expand Novavax access to children under 12. Next. We are still in a pandemic, and we need to act with urgency to protect our families and communities. Thank you.

Dr. Paydar: Thank you, Joaquin, appreciate your presentation very much. Next is Mr. Thair Phillips.

Mr. Phillips: Hi. My name is Thair Phillips, and I have no conflicts. I'm the spokesperson for Seniors Speak Out, a resource and sounding board for older adults, caregivers, and –

Dr. Paydar: Let me just interrupt you for a second. I need Devonte to please correct the slide on the left. Thank you.

Mr. Phillips: I want to thank the committee for your time and expertise today and throughout the Covid pandemic. So much has been accomplished, but, as we all recognize, there is still urgent work that needs to be done. As I now go about my daily life, like so many of my cohorts who are in their seniority, I have a new appreciation for normal. It is a normal we must assuredly want to preserve. I think it's human nature to want to push those difficult pandemic days out of our thoughts as we enjoy the present. And that's a good thing, but only up to a point. It's important, essential even, to remember that although Covid and its impact is, for most people, something that we want to be relegated to the past, something to be forgotten, if you will, the fact is that Covid is definitely not gone, and we must keep that in mind.

We have learned over and over again that COVID-19 is a virus which changes constantly and can find new ways to threaten our health. We must maintain our readiness against it. Every fall as days become shorter and cooler, we move inside. Kids return to school. Vacation time is over. And, like clockwork, respiratory illnesses start to take their toll on our lives. The past pandemic has reminded us how vulnerable older populations are to the ravages of respiratory diseases like flu, pneumonia, RSV, and, of course, Covid. As we who are in that age cohort know, prevention, beginning with vaccination, is our best defense.

CDC's statistics demonstrate how serious older adults have been in taking advantage of vaccine protection. As of April 2023, those statistics show that 95% of adults 65 and older have received at least one Covid shot, and 94% had completed a primary series, but that number declined to 43% for the updated bivalent booster. The VRBPAC meeting today is an important step forward in helping older adults understand the importance of getting a shot that offers protection for the current form of the COVID-19 virus. Like friends and family members of all ages, we know we need to get flu shots every fall because the strains of flu change every year. FDA's worth in highlighting the yearly changes in the COVID-19 virus and the necessity of keeping our protection up to date falls into line with preventive health measures older Americans are used to and regularly rely on. It helps to eliminate confusion and uncertainty and is a potent reminder that we can and need to take action to keep normal life normal. Thank you.

Dr. Paydar: Great. Thank you so much, Thair, for your presentation. We appreciate your participation in today's meeting. Next is Ms. Amy Harth.

Ms. Harth: Good afternoon. I do not have any conflicts to disclose. I'm here to ask the committee to relax your language around who can get a second bivalent Covid booster. When I tried to schedule a second bivalent booster, my doctor's office initially told me no. They said they're turning lots of people away because the FDA won't allow it. Restricting a second booster only to those 65 and older or immune compromised left me terrified and wondering why, when the shots are plentiful and broadly safe. I have a PhD in ecology, and I wish to remind the committee that population level statistics don't predict a specific individual's risk.

I'm 55 and have multiple medical conditions. None are considered immune compromised. However, I have a tenuous grasp on staying functional enough to work. I fear long Covid, because adding one more health problem could leave me permanently disabled. Not only would

that devastate me financially, it would force me to file for Social Security disability. I would far prefer staying productive and supporting myself. In August of 2019, a concussion left me temporarily unable to work. I live alone, and my only contact with people became the physical and occupational therapy appointments at my local hospital. That September, a hospital patient sitting next to me sneezed. Three days later, I became severely ill, and my epiglottis swelled, completely blocking my esophagus. If it had kept going, it would've shut down my airway, and I wouldn't be here talking to you.

I ended up in the ICU on dexamethasone. They didn't know whether the underlying infection was bacterial or viral. They simply did their best to stop the swelling, and we all kept our fingers crossed. I emerged from the hospital so weak I could barely walk or stay awake. Then an odd rash covered my trunk. A bit later, one of my toes turned purple, and I was perplexed. It didn't hurt, and I hadn't injured it. I also lost a lot of weight and hair, and a good year passed before I was fully recovered. I can speculate as to what happened to me, but the reality is that we will never truly know. What I do know is that immunity to Covid wanes significantly three to six months following an infection or immunization. The shots are safe, they're abundant, and I believe it's unethical to stop me from getting a second Covid booster when one sneeze almost killed me four years ago.

Many others want a second bivalent booster. I've spoken with people who had a rough time with a documented Covid infection or who have a condition that puts them more at risk and who want as much protection as possible. There are also people who live with an immune compromised loved one who want to do everything possible to protect them. The public health emergency is over. However, Covid has not gone away, and masking alone isn't enough. I'm doing everything I can to avoid infection. And, yes, I know the shots aren't perfect, but an

imperfect shot is surely better than no shot. For a lot of people, one shot a year might be enough. For many of us, however, your restriction is compromising our access to needed medical care.

Just because fewer people in younger age groups are dying doesn't mean that none of them are dying. Those losses are just as significant to their family and friends. Please change your language to allow anyone to get a second booster based on their unique circumstances. I further ask that you do the same whenever you find it necessary for anyone to get a booster. Restrictive language had a place when vaccine supply was restrictive, but we are no longer in crisis. And, again, population level statistics don't predict a specific individual's risk. Thank you.

Dr. Paydar: Thank you, Amy. Thank you for sharing your personal story and for participating in today's meeting. We appreciate it very much. Next is Dr. Katherine Matthias.

Dr. Matthias: Yes, thank you. I have no financial interest to disclose. My name is Dr. Katherine Matthias. I am a mother of two beautiful young daughters, a pediatrician, and a co-founder of Protect Their Future, a grassroots nonprofit organization dedicated to advocating for equitable healthcare and COVID-19 vaccine access for children. First of all, I would like to express my support of an updated COVID-19 vaccine from all three manufacturers. The more options given to the general public, the better uptake will be. That said, it is imperative that parents are given the choice to, once again, protect their children. I am asking this committee to approve booster doses for children of all ages at the same time as adults. I'm hoping that access to this booster will be available before school starts, which in some states is early August.

Exactly one year ago today, this committee was reviewing data regarding the COVID-19 vaccine trials for children under five and voting on EUA approval of the vaccines in this age group. That day was momentous for parents. Many of us had been pregnant at the start of lockdown, raised newborns in isolation, cared for rambunctious toddlers with little help from

friends and family, all while trying to juggle our own mental health and careers as the pandemic wore on. The delays in the vaccine trials and approval process had been soul crushing, but after nearly two and a half years of constant worry and pandemic fatigue, on this day last year, we were finally able to provide our children immunologic protection against COVID-19. We have come a long way since then. As of May 2023, 2.2 million children under five have received at least one dose of a COVID-19 vaccine. However, this number is dismal compared to other age groups. And with waning immunity, COVID-19 is still a threat.

The CDC website shows that as of June 7th, there have been a total of 765 deaths due to COVID-19 just in the zero to four age group. This means that since this time last year, COVID-19 has taken the lives of close to 300 babies and toddlers. These babies account for the majority of new pediatric Covid deaths reported to the CDC since last June. As you all know, that number is also much higher than annual flu deaths for all children under 18. It is clear young children, especially those under one year of age, are at significant risk of harm. Furthermore, you must consider complications that can arise from a COVID-19 infection itself, such as Type 1 diabetes, long Covid, and MISC, of which there have been nearly 9,500 cases since 2020, all of which can have devastating and lifelong consequences for children. A publication released by the AAP just last week demonstrated the outstanding safety profile of these vaccines. The study reviewed safety data collected from nearly 250,000 COVID-19 vaccine recipients under the age of five and found zero cases of myocarditis or pericarditis. Last week, the CDC also released a safety monitoring update for children zero to four, receiving a third dose of the vaccine using the VAERS and Be Safe data sets, and, once again, found no new safety concerns.

The last issue I want to address is the immense barriers parents have been facing in order to access COVID-19 vaccines for their children. Many offices are not stocking the vaccines, and

children under three cannot receive their vaccination at the pharmacy. Some parents are driving hours round trip to find a provider able to vaccinate their young children. It is no wonder why vaccine uptake is so appalling in this age group, despite the fact that every day babies are aging into eligibility, and, as we saw earlier, are at higher risk than any other pediatric age group. The access issue needs to be addressed immediately with state health departments and pediatricians. Single dose files would be a massive step in the right direction. This would help prevent administration errors, which now count for the vast majority of events reported to the VAERS system for kids. Children are our future, and we need to make their health and safety our top priority. Thank you very much for allowing me the privilege of speaking at today's meeting.

Dr. Paydar: Thank you, Dr. Matthias, for your participation and sharing your views with us today. Next is Ms. Karyne Jones.

Ms. Jones: Yes. Thank you. Good afternoon. I'm Karyne Jones, and I'm President and CEO of the National Caucus and Center on Black Aging. NCBA receives funding for non-branded health education and advocacy, and I have no personal conflicts or disclosures. NCBA also serves as a convening member of the COVID-19 Vaccine Education and Equity Project, a national coalition for more than 250 patient, provider, and public health organizations that have come together to advance public education and equity around COVID-19 vaccines. I want to thank this committee for your continued assessment of the evolving COVID-19 strains and analysis on how to ensure we have the most effective tools to protect against them.

The challenge before you is not a small one. While we know the uptake of COVID-19 vaccines initially was quite high, the adherence to recommendations for subsequent doses has been declining due to several factors, including misinformation, COVID-19 fatigue, and the continued lack of information and resources reaching underserved communities. Compound

these with the fact that public health emergency has now ended, and there is a serious risk that many Americans may not fully understand the threat COVID-19 still poses for our communities. We hear from the communities we serve that there is still a lot of confusion around who should be receiving another COVID-19 shot and when they should receive it. Especially for those older and immune compromised Americans who are most at risk of serious illness for this virus, providing clear and simple recommendations for remaining up to date with their Covid vaccine is really critical.

Last fall and winter, we were faced with quadruple threat of our respiratory systems, as COVID-19, RSV, influenza, and pneumonia converged, and we saw increases in hospitalizations and deaths as a result. Now we have an opportunity to get ahead of the upcoming respiratory virus season by informing the public now of the best ways to protect themselves before the season starts. We are extremely encouraged to see the FDA approve two new vaccines for RSV and today are hopeful to hear this committee discuss the right approach for ensuring science is keeping up with the pace with the current strains of Covid.

The community I represent is unfortunately still one of the hardest hit by this pandemic, which once again underscores the reoccurring and long lasting impact of healthcare inequity, older and underserved communities. During the 1918 Flu pandemic, black Americans were more likely to die compared to white Americans, and most recently during the 2009 HINI Influenza Pandemic, this population was more likely to be hospitalized and die than others. In our effort to reverse this trend, we focus on making sure that the information and the resources Americans need to make an informed decision about their health in reaching all populations. We leverage opportunities to ensure equitable access to these innovative tools, and we rely on the science and

taking time to understand what may be holding people back from remaining diligent in protecting themselves against this virus.

This committee can support our efforts by providing us with clear understanding of how the COVID-19 vaccines will evolve and why we should ensure we keep up to date with them. We look forward to continuing to follow this committee's recommendations, and we ensure that the latest information about the protective tools is made available broadly to every community so that individuals can be confident in their decision to stay up to date on their vaccines. Thank you.

Dr. Paydar: Thank you, Ms. Jones, for your participation today. We appreciate your presence. Next is Mr. Burton Eller.

Mr. Eller: Good afternoon. I have no financial conflict to report. The Grange is the only national organization who has, over its 156 years of existence, focused upon all aspects of rural life in rural America. In recent decades, advocating for access to quality healthcare has become vital part of the work we do in small towns and rural communities throughout the country. We are most grateful for the opportunity to speak here today, and to, once again, thank this committee and the FDA as a whole for their service in protecting the health of our country.

As we have noted before, rural citizens face enormous health disparities by virtue of where they live. Among the more significant are lack of access to care in rural America is estimated to account for 55% of preventable hospitalizations or deaths from all causes. On average, rural life is two years shorter than that of urban residents. Rural hospitals disappeared at an alarming rate. At least 200 have closed in less than 10 years, and 1/3 of those remaining have grim prospects for survival. Men, women, and children living in rural America have higher rates of illness for many conditions, from pneumonia and flu to certain types of cancer and obesity.

Getting healthcare in rural America requires traveling greater distances, taking more time away from work, and waiting longer for appointments because of provider shortages.

The National Grange, its state Granges, and its 1400 local Grange chapters around the country work together to solve some systemic problems that negatively impact rural life, such as those I have just mentioned. To that end, we have, throughout the COVID-19 emergency, worked to inform our members and neighbors about the importance of vaccination in protecting their health and how, when, and where to access vaccination and treatments. However, we know rural Americans experienced a disproportionate impact from COVID-19, many of which were related to the disparities we have mentioned in these remarks. We also know there is confusion among many in our communities about how prevalent Covid is and whether they should still be taking steps to protect against it. For these reasons, we are encouraged by the discussion around potentially offering the COVID-19 vaccine on an annual basis, similar to the flu shot, and we urge this committee to provide as simple and straightforward guidance as possible on who should consider receiving this updated vaccine.

Rural citizens don't have a standalone pharmacy or a grocery store with a pharmacy just down the street. We don't have urgent care just a few minutes away, and we probably can't get an appointment in the next few days. Making it possible for rural citizens to make the most of their annual provider visit and plan ahead will absolutely help boost vaccine rates, protect health and save lives and money. The National Grange stands ready to help advance health options for rural America, and thanks FDA for its excellent work in seeking ways to prevent COVID-19 from ever again taking such a toll, building in ways to help each of us understand what we need, when we need it, and making it possible for us to do it in ways that maximize the options available where we live and work. These are keys to success. Thank you.

Dr. Paydar: Thank you, Mr. Eller. We really appreciate your participation today. Next is Ms. Robin Strongin.

Ms. Strongin: Good afternoon. My name is Robin Strongin, and I direct health policy for the National Consumers League. I don't have any conflicts. Since our founding by renowned social reformer Florence Kelly in 1899, NCL has had a long history of supporting consumer access to preventive medicine and lifesaving medical interventions. Looking back over the last three plus years of a global pandemic, we have been encouraged by the way scientific advancements have been evolving right along with the virus. The development, evaluations, and approval of the first generation of Covid vaccines enabled us as a society to resume our lives in so many ways. And as we have experienced how new strains of the virus impact our communities in different ways, we are grateful to have preventive and treatment options available to combat these.

While, thankfully, most Americans received the initial Covid vaccines to protect themselves from serious illness and death, we know that number drops off considerably for subsequent booster doses. We cannot allow society to become complacent. The public health emergency may have ended, but Covid is still circulating within our communities whether we want to admit it or not. That is why the work of this committee is so important, as we look to you to evaluate the current threat of Covid and the impact it could have heading into the 2023 respiratory virus season. Consumers may be tired of hearing about Covid, but that does not dilute the impact this committee can have by offering clear and common-sense guidance for protecting ourselves against the next strain of Covid.

Since it seems likely COVID-19 is here to stay, we appreciate the committee's discussion around whether the vaccines will be treated in the future similarly to the flu vaccines and offered on an annual basis. Encouraging Americans to receive their annual vaccines before the fall and

winter months has proven an effective and efficient process for not only protecting individual health, but also in reducing the spread of these potentially deadly viruses within communities. Following a more annual schedule can also help to address consumer's confusion on when they should consider receiving their next Covid vaccine.

For our part, the National Consumers League will continue to focus on educating on the latest information and resources available for these vaccines and supporting steps to ensure broad and equitable access to them. As you know, we cannot effectively address COVID-19 unless all communities understand the value of prevention and are willing to take action to protect themselves. We thank this committee for your ongoing efforts to ensure Americans have the most effective and safe options to protect themselves against respiratory illness, and we will continue to work alongside you to inform and guide consumers. Thank you very much.

Dr. Paydar: Thank you, Ms. Strongin, appreciate your participation. Last, but not least, is Ms. Elle Pierce. Go ahead.

Ms. Pierce: Hello, and good afternoon. My name is Elle Pierce, and I'm grateful for the opportunity to speak before the committee today. I have no conflicts to disclose. As a mother of two incredible toddlers, a wife, and a pediatric registered nurse, I'm here today to advocate for unrestricted, widespread access to Novavax, expedited clinical pediatric trials, and authorization of Novavax for our pediatric population under 12. Additionally, I request timely distribution of all updated vaccines once they become available. Throughout this pandemic, we have repeatedly been told we have the tools to combat COVID-19. However, access to one of our most effective tools, the Novavax vaccine, is needlessly restricted. As we continue efforts to end the pandemic, it's essential to revise Novavax eligibility criteria to ensure access to as many individuals as possible, including those who wish to restart a Novavax primary series.

For many individuals, Novavax is the preferred choice over the alternatives. Multiple clinical trials have shown it to be safe and well tolerated, including for participants who have previously received mRNA vaccines. Due to this evidence, numerous other countries have approved Novavax booster shots, irrespective of prior mRNA vaccination status. For individuals unable to tolerate mRNA vaccines, such as those with PEG allergies, Novavax is the only option. Because Novavax uses a conventional protein-based platform that is familiar to most people, it's also a viable alternative for those who are hesitant to receive mRNA vaccines.

Novavax has the ability to alleviate strain on healthcare systems, save lives, reduce long-term Covid complications, and help society regain a semblance of normalcy. It offers outstanding efficacy, safety, and adaptability, making it an indispensable tool in our fight against COVID-19. If our goal is to increase vaccination rates, we must eliminate bureaucratic roadblocks and simplify the process for those wishing to safeguard themselves. As we continue our battle against Covid, the United States must prioritize the health and wellbeing of our vulnerable children. Despite prevailing misinformation that suggests children are spared from the virus, it's crucial to acknowledge that they are not immune to its impact. Considering this, I urge the medical and scientific communities to expedite clinical trials of Novavax for expanded pediatric use.

With the vaccine's established record of safety and efficacy in adults, we have a solid foundation for evaluating its effectiveness in children. To accelerate the process, we should leverage knowledge and experience from previous trials, streamline protocols, and foster collaboration among researchers. By expediting Novavax pediatric trials, we can provide an additional layer of protection for our children. Due to the fact that Covid is not a seasonal virus, nor is it over or gone, I'm asking the committee to make the updated formulations of all Covid

vaccines widely available and easily accessible as soon as they're available. Our children deserve protection before the school year begins this August. Any time after that is too late.

In summary, I'm respectfully requesting this committee immediately ease restrictions around eligibility for current and future Novavax formulations for the wider population. It's imperative we allow people to restart a new primary series with Novavax, irrespective of vaccine histories, and permit boosters without waiting for regulatory approval for individual shots. Finally, by extending Novavax access to our youngest children, we can protect them from the devastating effects of COVID-19 and contribute to the collective effort of overcoming this global crisis. Novavax merits your full attention and support. Thank you.

Dr. Paydar: Thank you, Ms. Pierce. Thank you everyone once again for participating in today's advisory committee and for sharing your views and comments. This concludes the Open Public Hearing session for today, and now I hand over the meeting back to our chair, Dr. Monto. Dr. Monto.

Dr. Monto: Thank you, Sussan. Next, we're going to hear the FDA presentation, considerations, and recommendations for changes to COVID-19 vaccine strain composition. Dr. Jerry Weir, Director, Division of Viral Products, FDA. Dr. Weir.

FDA Presentation: FDA Considerations and Recommendation for Changes to COVID-19 Vaccine Strain Composition — Dr. Jerry Weir

Dr. Weir: Oh, thank you, Dr. Monto. The committee has heard a lot of data today. I'm not going to add more data for you to digest, but rather summarize at a fairly high level what you've heard, as well as briefly review the process that we've used at the FDA over the last few months to evaluate this data in support of strain selection. Next slide. Starting with some background, most of you on the committee have been here over several years actually, and you're aware that we have met three times to date to discuss strain composition of COVID-19 vaccines in the US.

We met first over a year ago on April 6th, 2022, to have our initial discussion about the framework for updating COVID-19 vaccine composition process. At that initial meeting, there was general agreement that COVID-19 vaccine strain composition decisions should be data driven, and that there should be evidence to indicate that a proposed modified vaccine composition would likely provide improved effectiveness compared to current vaccine compositions.

We met again a few months later on June 28th, 2022, and at that time we discussed whether an updated COVID-19 vaccine strain composition was needed, and the committee voted to include a SARS-CoV-2 Omicron component for COVID-19 booster vaccines. At that meeting, there was a general preference for a bivalent vaccine containing the ancestral and the Omicron strains. More recently in January, on January 26th, the committee met again and had additional discussions about the approach to the periodic updates of COVID-19 vaccine strain composition. To summarize briefly, that meeting there was, as far as the strain composition discussion, there was general agreement that there should be a periodic assessment by the FDA and the VRBPAC to reassess the current vaccines and decide if improvement is needed, also that updating the strain composition of COVID-19 vaccines would likely be a continuous process, and further that a late spring or early summer target for a FDA VRBPAC review and recommendation seemed reasonable and practical for delivery of an updated vaccine for a fall vaccination campaign.

So at this time, I want to step back to that June 28th meeting to review what we did at the time, because I think it's both, one, this is only the second time we've gone through the strain composition update decisions, but I think what we did at that meeting a year ago was instructive for what we did then versus make some nice comparison to the choices that we're faced with now. You can go to the next slide. I have two or three slides about that meeting.

Okay. As I said a minute ago, we met on June 26th, 2022, to consider whether a change to the current COVID-19 vaccine strain composition was needed. The committee voted to recommend the inclusion of an Omicron component for booster vaccines in the United States, but also at that meeting we discussed the evidence supporting a monovalent Omicron or a bivalent vaccine, which would be the prototype, or the original strain plus Omicron, and the committee discussed the selection of specific Omicron sublineages to be included in the vaccine. Specifically, they discussed the possibility of including a BA.1 component or a BA.4, BA.5 component. And a few days later, on June 30th, the FDA notified vaccine manufacturers of FDA's recommendation to develop a bivalent vaccine that included the original strain plus an Omicron BA.4/5 as a booster dose to improve protection.

The first bivalent vaccines from Moderna and Pfizer BioNTech were authorized for use in individuals 18 years of age and older, and 12 years of age and older, respectively, on August 31st. So the next slide shows the situation we were faced with last June. On the left is a little hard for you to read, but it's a dendrogram that I showed at that time at the meeting. And what that showed, as you see on the right with the variant proportions, was that the virus was evolving since the emergence of Omicron into both BA.1 and BA.2 viruses. And our discussion at the time concerned the selection of Omicron sublineage variants, BA.1 versus BA.4/5. The reason that was the choice that we were confronted with was because at the time of this meeting, manufacturers had produced and evaluated BA.1 vaccines in clinical trials, and they were prepared to supply a BA.1 containing vaccine for 2022 and 2023.

It's also true that at the time we did not have perfect global alignment. The WHO had recommended a BA.1 vaccine, as had our European colleagues. But the fact is that at the time we were having this meeting in June, BA.1 was no longer in circulation. At that time, it had been

supplanted by other BA.2 derived viruses, and this is shown in more detail on the next slide. This is a sort of linear representation of the spike protein with listed amino acids. The reason that the change from BA.1 to BA.4/5 was the decision that we had to make, as I said, we had data for BA.1. Manufacturers were prepared to make this, but BA.1 not only didn't exist, but BA.1 was a lot different than BA.2 and the derivatives that were coming from BA.2. Specifically, I have them listed on the right of this slide.

There were major differences between BA.1 and BA.2 spike proteins. Nine amino acid changes, three deletions, and one addition in BA.1 that were not present in BA.2. Seven amino acid changes and one deletion in BA.2 were not in BA.1. So these two Omicron derived viruses were quite different from each other. On the other hand, there were fairly minor differences between BA.2 and the BA.2 derivatives, BA.2.12.1 and BA.4/5. Those are shown near the bottom of the slide on the left. You see that BA.2.12.1 only had two changes relative to BA.2 and BA.4/5 only had three or four. It actually had one deletion that was present in BA.1. So that was the situation we were faced with. BA.1 was extinct or essentially extinct. It didn't exist. And BA.2 derivatives such as BA.4, BA.5 were the predominant circulating strains. So if you move to the next slide, we'll talk about now where we are today.

Both a year ago and now, we listed considerations for modifying COVID-19 strain compositions for COVID-19 strain composition decisions. The key questions that were posed then that we felt needed to be addressed by the agency and the VRBPAC in considering whether to modify the COVID-19 vaccine composition are, one, are there SARS-CoV-2 virus variants circulating that are antigenically distinct from the strain included in the current vaccines? Have currently circulating SARS-CoV-2 virus variants become or are they expected to become dominant and displace earlier virus variants? Three, is there evidence that current vaccines are

less effective against new circulating virus variants than against previous strains of virus? And four, is there evidence that a candidate vaccine with an updated strain composition will be more effective against these new circulating virus variants and provide an improved clinical benefit?

I have one slide that mentions a summary of the effectiveness. That's on the next slide. Okay. So you've heard a lot of data already about this from our CDC colleagues, as well as you heard data from each of the manufacturers as far as the current effectiveness of authorized COVID-19 vaccines and the need for a periodic strain update. First of all, observational effectiveness data strongly suggested that updating the composition of the COVID-19 vaccines in 2022 from the original monovalent to a bivalent containing the original and Omicron BA.4, BA.5 components offered benefit and protection from COVID-19 disease caused by Omicron. I think the data is pretty clear that there was a benefit to this. Nevertheless, as you also heard today, there appears to be an inverse relationship between the time since vaccination and vaccine effectiveness, such that bivalent COVID-19 vaccine effectiveness against the evolving Omicron sublineages appears to wane over time.

This appears, from the data presented by CDC, that this may be even more true against virus variants such as XBB derivatives. Three, the data indicate that bivalent COVID-19 vaccines elicit improved variant specific neutralizing antibody titers, but these antibody titers also decrease over time after vaccination, and they are substantially lower against more recently circulating strains of virus like the XBB vintage viruses. Taken together, as far as effectiveness, the available data suggests that an updated strain composition of COVID-19 vaccines that will more closely match currently circulated XBB lineage viruses may be beneficial. Next slide.

Okay. So in January, we outlined the approach that we would use for vaccine strain composition recommendations. And as we outlined and proposed at that meeting, the evidence

used to determine the need for updating the strain composition of COVID-19 vaccines would ideally include multiple types and sources of data. Over the last few months, the FDA has reviewed various types of data. It is listed below, and I'm going to walk through these in the next few slides. We've reviewed this data. We've engaged in key partners generating this data, and that included both vaccine manufacturers, other government agencies, as well as experts in the field.

But if you break it down, the type of data can be grouped into a few categories. One is virus surveillance and genomic analyses to identify emerging new virus variants, antigenic characterization of viruses to identify antigenically distinct variant viruses, post-vaccination human serology studies to evaluate the antibody responses generated by current vaccines against more recently circulating virus variants such as XBB lineage viruses, and, finally, preclinical immunogenicity studies to evaluate immune responses generated by new candidate vaccines, for example, those expressing or containing updated variant spike components against antigenically distinct circulating virus variants. In addition to reviewing all of these types of data, FDA reviewed the discussions and recommendations put forth by other regulatory groups and public health agencies. And, finally, the FDA has discussed manufacturing timelines with each of the manufacturers of authorized and approved COVID-19 vaccines to understand the impact of a strain composition recommendation on vaccine availability.

So I'm going to give you a quick, high-level overview of our review of each of these types of data, but first I want to take a pause in one slide, the next slide, to talk about the role and the use of virus neutralization data to inform vaccine strain selection. The reason for this is because in much of the types of analysis that we do and the types of data we look at, virus neutralization data plays a key role. Virus neutralization data are routinely used to establish antigenic relationships among contemporary viruses. We also use virus neutralization data in

post-vaccination studies, and we also use neutralization data to evaluate candidate vaccines in preclinical studies. Although other immune mechanisms are important for protection, and protective neutralization titers are unknown and are likely to vary among virus platforms and for different virus variants, neutralization has been shown to correlate with protection for all spike based vaccines.

I know everybody here has seen this graph that came from The New England Journal of Medicine paper that basically plotted in all of the phase three trials conducted in the first years or so of the pandemic that showed essentially what I just stated, and that is for all of these spike based vaccines, higher levels of neutralizing antibody correlated with higher levels of protection. I do want to mention in the sub-bullet that the neutralization assays used by manufacturers of authorized and/or approved Covid vaccines have been reviewed and evaluated by the FDA. So the reason I mention this is because we feel like this is still the strongest marker we have that is useful for informing vaccine strain selection.

Now if we go back to the type of data reviews, the next slide, as I said, one of the key types of data, of course, is virus surveillance and genomic analysis. You heard a lot of this from CDC but also from WHO and the manufacturers. The left shows the dendrogram of current virus evolution. I think this was also shown by WHO, but basically it says what you've already heard is that the virus continues to evolve. Almost everything has evolved now from original BA.2 viruses and now specifically from XBB recombinant viruses. The graph on the right is similar to the one shown by CDC, but it shows the percentages of different XBB viruses that are currently circulating. XBB.1.5 is decreasing in proportion, 1.16 seems to be increasing, as do, in the very bottom, other XBB lineage viruses such as 2.3. But the point is that in June of 2023, over 95% of all isolates everywhere are XBB sublineages. Next slide.

So what do we know about these XBB viruses? Well, we do have some virus characterization now. This slide is similar to one I showed you that we used last year, but specifically now focuses on the XBB lineage viruses. Once again, the top two rows show mutations in BA.1 and BA.2 compared to original Wuhan like viruses, and the specific BA.2 viruses in line two mutations that are specific for BA.2. Now, as you've already heard, and you know by now, XBB is a recombinant of two BA.2 derived viruses, BA.2.10.1 and BA.2.75, although there are substantial spike amino acid changes compared to BA.2, including multiple RBD mutations.

In response to a question that was brought up earlier in the day, and I think it was by Dr. Meissner, recombinations have occurred before this XBB. They've occurred throughout the pandemic. It's just that until these particular recombinants appeared, the other recombinants that were isolated did not appear to take off. So, anyway, it is a fairly common phenomena among Coronaviruses. Finally, in this slide, XBB has continued to evolve with accumulation of small numbers of mutations in the spike in terminal domain and the RBD. This is shown in green at the bottom. First of all, the first line shows the XBB mutations compared to BA.2, which, as I said, had quite a few amino acid changes compared to BA.2, and hence BA.4/5, that were in last year's vaccine. XBB.1.5 has a couple of amino acid changes compared to the original XBB virus. And then XBB.1.16 and XBB.2.3 have other amino acid changes. These differ from XBB.1.5 by one amino acid each in the RBD, and I box those in the bottom two rows. But, of course, what that means is XBB.1.16 and XBB.2.3 differ from each other by two key amino acids in the RBD.

The next slide shows a final little summary slide of what we know about virus characterization about the XBB lineage SARS-CoV-2 viruses. As I've already mentioned, genomic analysis suggests a close relationship among the XBB lineage viruses. Antigenic

characterization of circulating XBB lineage viruses is limited to a few recent studies, but also suggests antigenic similarity among the XBB lineage viruses. In one study, sera from XBB.1 infected hamsters, which is a mono-specific sera, neutralized XBB.1 and XBB.1.5 and XBB.1.16 pseudoviruses to a similar extent, but poorly neutralized pseudoviruses expressing earlier spike proteins. This particular reference and the key graphs from that study have been shown twice already this morning. So I'm sure you've seen that.

Several studies, including those presented at this VRBPAC, by manufacturers of authorized or approved COVID-19 vaccines show substantial decreases in neutralizing antibody response against XBB subvariants. Data from preclinical studies, and I am going to talk just a bit more about preclinical studies, as well as clinical studies in a minute. But data from preclinical studies with XBB.1.5 and XBB.1.16 candidate vaccines, which were conducted by manufacturers of the authorized approved vaccines, indicate substantial cross neutralization between XBB.1.5 and 1.16. Cross neutralization was also observed against XBB.2.3, although it's a somewhat more limited data set, although actually there's more data that's been generated since I made this slide, and that was presented by the different manufacturers earlier today. And, finally, there's preliminary data from one clinical study with an XBB.1.5 candidate vaccine that also indicates substantial cross neutralization between XBB.1.5 and XBB.1.16.

If we go to the next slide, this is a high level summary of post-vaccination human serology studies. Post-vaccination human serology studies are used to evaluate antibody responses that are generated by current vaccines that gets more recently circulating virus variants. The COVID-19 vaccine manufacturers are well positioned to generate the robust data needed from post-vaccination human serology studies. I just want to remind you that sera are available only from recipients of current vaccines or infected individuals. In other words, except

for the one study that Moderna described, none of the sera from these subjects have exposure to an XBB vaccine, and there's only limited exposure to any XBB lineage viruses in this study. The neutralization titers measured in this post-vaccination human serology studies against new virus variants, such as XBB.1.5 and 1.16, can only indirectly suggest similarities or differences between the variants.

The data presented at this VRBPAC by these manufacturers of authorized approved COVID-19 vaccines indicate that recent virus variants, particularly the XBB descendant lineage viruses, are especially resistant to neutralization by antibodies, elicited by prior vaccination and/or infection. Besides the results presented by the manufacturers, there are similar results showing substantial reductions in neutralizing antibody titers against XBB lineage viruses and recipients of current vaccines that have been reported in many other studies. And I think the WHO presentation listed several of these. I've listed only one more, and this was results from an NIH COVAIL clinical trial. And the only reason I mentioned that is because the assays they use are also assays that have been submitted and reviewed by the agency. Next slide.

Okay. I wanted to talk briefly about high level view of the preclinical immunogenicity studies with new candidate vaccines. Preclinical immunogenicity studies are used to evaluate immune responses generated by new candidate vaccines, those expressing or containing updated variant spike components and used to evaluate against antigenically distinct circulating virus variants. Preclinical immunogenicity data, which is almost always neutralizing antibody, can provide an indication of how well antibodies to the spike of one strain will cross neutralize other variant strains as SARS-CoV-2 and thus help inform strain selection in combination with other data. It is not predictive of protection. It just gives us an indication of cross neutralization.

These studies, of course, are dependent on COVID-19 vaccine manufacturers producing candidate vaccines at risk and conducting the studies to generate the data for evaluation. And I think it's very gratifying to see that all three of our vaccine manufacturers actually produced a lot of candidate vaccines and did quite extensive studies in a very short period of time. The data presented by these manufacturers indicate that updated XBB monovalent formulations of candidate vaccines elicit stronger neutralizing antibody responses against XBB descendant lineage viruses than current bivalent vaccines. So that is the summary of where we are now with the data that we've reviewed over the last few months.

In the next slide, I want to briefly mention something that comes up at all of these meetings and that is important, and that's the global alignment of COVID-19 strain composition recommendations. As you probably know, there are many challenges to the global coordination of the COVID-19 vaccine strain composition. A lot of this is due to, basically, the virus doesn't cooperate very well. It doesn't spread uniformly around the world, and different parts of the world have different considerations and different things that they have to consider in making a recommendation. Nevertheless, global public health agencies and vaccine regulators meet throughout the year in an effort to align the criteria used for evaluation, as well as the vaccine strain composition recommendations when possible.

I listed three different things that have happened over the last few months. One is the WHO Technical Advisory Group, the TAG-CO-VAC, which we heard an entire presentation from about their review and their recommendation. That's summarized in one quick sentence. One approach recommended by the TAG-CO-VAC is the use of a monovalent XBB.1 descendant lineage, but also there have been other groups, the International Coalition of Regulatory Authorities. This is an informal group of international regulatory authorities, which we're one,

met in early May to discuss the antigen content of COVID-19 vaccines. And one quick line from their statement, XBB is considered an adequate candidate for vaccines composition update.

And more recently, just about a week ago, the European Center for Disease Prevention and Control and the EMA issued a statement on updating COVID-19 vaccine composition for new SARS-CoV-2 virus variants. Elements from their statement were that one monovalent vaccine composition is suitable to ensure adequate immunogenicity against circulating SARS-CoV-2 in both primed and naive individuals. And also the inclusion of a strain belonging to the XBB family of Omicron subvariants is adequate to ensure cross-reactivity against current dominating and emerging strains. So in spite of the challenges, regulators and public health authorities do meet, and we do try to coordinate when at all possible. Next slide.

So before I summarize the main elements from this presentation, I wanted to make a couple of comments about future directions. One of which is that I think it's obvious to all of us now that updating the SARS-CoV-2 strain composition of COVID-19 will be a continuous process. It would be great if it wasn't, and that it was stable. But it doesn't look like it now. Whether the rate of change will continue, none of us know, but we have to be prepared that this is going to be a continuous process. There are many challenges and uncertainties that remain. You could probably make a long list.

I mentioned two here that I just wanted to highlight. One is understanding and improving the durability of protection from vaccines. The second challenge that remains is understanding how differences in neutralization titer actually correlate to clinical outcomes. Again, this is not like the influenza situation where we have a pretty good field that if you see a reduced neutralization or HI titer of two-fold, four-fold, eight-fold, you know what the clinical outcome is, how the clinical outcome is affected. So we need more understanding about this. It's also true

that we need improved coordination, and this possibly includes additional resources, but this improved coordination is needed to generate the quality data that's needed for strain composition decisions. I've listed several examples here. There may be more.

One is a timely production of mono-specific animal sera, for example, hamster sera. And this is useful and important for determining antigenic relationships among contemporary circulating viruses using standardized neutralization assays. Right now our sources of this mono-specific sera are very limited and usually not, in a sense, timely enough to make a strain composition decision. We also need additional sources of human sera from recipients of current vaccines to evaluate the need for an updated vaccine composition. Right now we have sources of sera from the vaccine manufacturers, which is great, but it would be good to have additional sources from other places.

I'm reminded of the influenza situation where we routinely have sera from pediatrics. We have them from adults. We have them from elderly. And those are evaluated by different WHO centers. So, anyway, additional sources of human sera would be important. Also, additional sources of human sera from individuals infected with contemporary circulating viruses is important to have for qualifying and standardizing assays. And, finally, the last one that I've listed here, which is a bit aspirational, I'll admit, is that there needs to be a better and independent and reliable risk assessment of circulating virus variants to focus resources and better predict the need for an updated vaccine composition. So I'm almost at the end.

The next two slides are a quick summary of where we are and everything you've heard. By several measures, including escape from antibody neutralization and waning protection, current COVID-19 vaccines appear less effective against currently circulating virus variants, for example, the XBB lineage viruses, than against previous strains of viruses. The manufacturers of

authorized approved COVID-19 vaccines have been evaluating updated candidate vaccines at risk. And, as they've all stated at this meeting, they are prepared to provide an updated vaccine for 2023-2024. But, as you've also heard, some of these manufacturing timelines may be impacted by the final choice of vaccine antigen. Next slide.

Last three summary points. Preclinical data from three different vaccine manufacturers all indicate that updated XBB monovalent formulations elicit stronger neutralizing antibody responses against XBB descendant lineage viruses than current bivalent vaccines. That available data strongly suggests that inclusion of an antigen from early strains of SARS-CoV-2, for example, Wuhan, in an updated vaccine formulation is unlikely to enhance the response to current virus variants. Preliminary data from a clinical study with one XBB.1.5 candidate vaccine also indicate improved neutralizing antibody responses against XBB descendant lineage viruses. And the totality of all this available evidence suggests that a monovalent XBB lineage virus vaccine is warranted for the 2023-2024 vaccine campaign.

That's the end of the talk. The next two slides have the voting question and the discussion topic, if you want to flash them up real fast before we just take questions and go into our discussion. This is the voting question. You saw it earlier in the day. And this is the discussion topic. So we'll come back to those, I'm sure, in a few minutes. Over to you, Dr. Monto.

Additional Q&A for CDC, FDA, and Sponsor Presenters

Dr. Monto: Thank you, Dr. Weir. Very comprehensive and clear presentation to put us ready for our later discussion after we have some questions. And I see Dr. Levy has his hand raised.

Dr. Levy: Thank you for that efficient review, Dr. Weir. A lot of information you're taking into account. This topic has been brought up several times before, but what is FDA's current view of what the correlative protection is to protect against coronavirus, infection, and disease? Is there any position of FDA in terms of asking sponsors moving forward to collect more T-cell

data? Do you want, in future meetings, to be summarizing those kind of data as well? These are questions for you as you summarize immunogenicity considerations. Thank you.

Dr. Weir: Okay. So to take them one at a time, I'm not sure that there's a unified view of correlates of protection. I think you've seen the data that's been presented that, in general, neutralizing antibody correlates with protection. That does not mean that there is some threshold that we can identify that says that this level you are protected. Most of those studies were done early in infection when Wuhan and Wuhan-like viruses circulated. Whatever the correlates of protection were then are probably not the same as they are now. And as I mentioned in one slide, I think correlates of protection for antibody probably almost assuredly vary from platform to platform. Again, today at this meeting, we're using neutralizing antibody as a measure for something that informs strain selection. Ideally, of course, one would love a correlate of protection that one could point to and flash up a slide that says it's this level of antibody, or it's this level of something else. I don't think we're there yet. Although, again, a lot of people have different opinions about that.

I think the second part of your question was how do we feel about T-cell analysis? I would love to be standing here next year and telling you that we have more information about T-cell responses and what correlates with protection. I don't think we're there yet. We always encourage manufacturers to do these studies, but they're difficult. I don't think anybody should sugarcoat that. Doing a T-cell analysis and trying to correlate the type of T-cell measurement that you have with protection is very difficult. All T-cells are not the same. All vaccines don't elicit the same type of T-cell. So, yes, we encourage it. We look at it. As more data becomes available, we'll certainly use it.

Dr. Monto: Okay.

Dr. Levy: Thank you.

Dr. Monto: Just keep in mind, as we go through the question session, that if you have questions of the manufacturers of CDC, this is the time to bring them up. We'll have a discussion of the voting question and the rest after the break. So, Dr. Chatterjee, I think your hand was raised.

Dr. Chatterjee: Yes. Thank you, Dr. Monto. My question actually is for Dr. Dubovsky from the Novavax presentation. It is with regard to a slide that he presented. I believe it's VS-9, Dr. Dubovsky, I was intrigued to see that the response in mice that were boosted with XBB.1.5 was actually greater against XBB.1.16 than when they were boosted with XBB.1.16. Do you have an explanation for this phenomenon?

Dr. Dubovsky: Yeah. You may have spotted similar responses in some of the other sponsor's presentation. XBB.1.5 is a very good immunogen. It really does its job well. Some of these differences may be due to group sizes, right? So these are groups of 10. So there may be some changes. This is a bioassay, so it's less precise than, for instance, receptor binding inhibition.

Dr. Chatterjee: Okay. Thank you. Because that was going to be my follow-up question on VS-14, but that makes sense given what you just said. So thank you very much.

Dr. Monto: Thank you. Dr. Gellin.

Dr. Gellin: Thanks. Jerry, that was an incredible recount of a lot of history that many were a part of. And thanks especially for sort of bringing us up to speed of what the other regulators were thinking about. In all of those discussions, have there been any discussion about dose? If I saw the slides correctly, the Moderna data showed that the bivalent immune response was similar to the monovalent immune response, even though the dose was different. And Kanta made the

point that monovalent would give you a more robust immunity. So is there a summit work on optimizing the dose between immunity and maybe reactogenicity? And then for the manufacturers, does it matter? In your hands, do the different XBBs perform differently so that you have some flexibility in picking among them for yield and other manufacturing issues? Thanks.

Dr. Weir: So I think you asked both me and the manufacturers some questions in that question. I'll start with the first one, but it was partly Moderna's data. Yes, there were some data presented, and I've seen other data in the literature too, that the differences in responses between a monovalent and a bivalent were probably not as much as maybe some of us would've predicted. For example, you don't always get two times as much a response to the variant component as you do in a monovalent, as opposed to a bivalent.

But that being said, no. I don't know that a lot more has been done to optimize the response. I do think that taking out the ancestral strain will do something to optimize the response, simply because you won't be competing with something that people have already seen two, three, four times. So I think that will help in the optimization. As far as optimizing dose, again, at this level, after a company sponsor has been approved or authorized or licensed would be a lot of clinical studies, so I don't know how much they're willing to invest in that. But I will basically turn it over to the sponsors to answer that part of your question.

Dr. Das: Thank you for that. And so I'll put up our clinical data again from the XBB.1.5 monovalent and the bivalent vaccines. Can I get CO-25 up, please. Yes. And as you said, you know, both the monovalent and the bivalent vaccines have a very good response against XBB.1.5 and a good cross neutralization response against XBB.1.16. And the response is numerically higher as well in terms of the GMTs and the fold rise for the monovalent.

In terms of the dose optimization, can I have the systemic reactogenic slide, please. So both of these doses are our standard 50 microgram dose for the booster. And if I have this slide up as well, our reactogenicity for these vaccines is actually quite, the reactogenicity is well tolerated. And it's very similar to that which we had for the bivalent vaccine booster, as well as the monovalent vaccine booster. So overall, very consistent with a very good immune response for the monovalent XBB.1.5 vaccine.

Dr. Monto: Thank you. I think Pfizer wishes to comment, please.

Dr. Swanson: Kena Swanson. Pfizer. If I could have slide one up, please. Just to follow up on the question around the mono versus bivalent, these are the preclinical data showing XBB.1.5 monovalent versus 1.5 bivalent. And this is a fourth dose booster. So in the context of two original vaccine doses followed by the current bivalent BA.4/5, so trying to more faithfully reproduce the current immunological setting. So in that context, we do also see a trend for higher neutralizing titers with the monovalent formulation compared to bivalent. And going back to the prior clinical data that we've generated, we've seen this also in humans when we initially evaluated the Omicron BA.1 monovalent versus bivalent vaccine. And the question around the dose level, we have evaluated 30 microgram versus 60 microgram. There is a subtle trend of higher neutralizing titers going from 30 to 60 microgram, but it's not a substantial increase. So I think the collective data is showing that the current dose level is sufficient for the variant adopted vaccines.

Dr. Monto: Thank you. Okay. Dr. Offit.

Dr. Offit: Yes. Thank you. So these vaccines will be available presumably in the next few months. The data that we don't currently have is we don't have either immunogenicity data or safety data from either Novavax or Pfizer. We don't have concomitant use data for either

influenza vaccine, which is likely to be given around the same time, or for older Americans, the RSV vaccine. And we don't have dosing data for young children who would be at risk and would benefit. So my question, I guess, to the FDA and to Jerry, is what exactly is the standard that you're going to be holding these companies to, to provide that information before clinicians are being asked to give this vaccine? Thank you.

Dr. Monto: Dr. Weir.

Dr. Weir: Yeah. Okay. So that's a little different from what we're talking about today about what should be in the vaccine, but it is true that, as we outlined in January, we expect, once a recommendation is made, an extensive data package from each manufacturer to support their vaccine. Things that you mentioned, like concomitant studies, all of those would be discussed with manufacturers. They would be prepared, I'm sure, to do the studies that we would need to evaluate that type of situation. I forgot the second part of it.

Dr. Offit: Dosing for children. Was there any interest in providing dosing for children?

Dr. Weir: Yes. So that, again, I can turn to my other FDA colleagues, but those discussions are underway between the agency and each manufacturer about doses for different age groups. So, yes.

Dr. Offit: But those data will, Jerry, you're anticipating those data would be in hand by the time this vaccine was rolling off the shelves. Is that fair?

Dr. Weir: I'm not sure I can comment right now on the timelines of all of this. Sorry. I don't know if Dr. Kaslow --

Dr. Monto: Anybody else, Jerry?

Dr. Weir: -- would something about the timelines for that or not. We do have a lot of submissions in house on different age groups and different doses and things that are under review now.

Dr. Monto: Okay. Should we park that question and come back to it later if there is an answer?

Dr. Offit: That makes sense to me, Dr. Monto.

Dr. Monto: Thank you. Dr. Rubin.

Dr. Rubin: Thanks. Dr. Gellin sort of preempted my question, but I do want to follow up then on the response to that one. The two doses that are used in monovalent and bivalent vaccines are very similar to one another. I mean, they're double the dose, but that is a rather small difference. Given that most of the population has seen multiple doses of antigen, in traditional immunology, if you wanted to improve the quality of antibody, you'd lower the dose of antigen rather than increasing it within this narrow range. So really, I think it's a question for the manufacturers. Do lower doses actually give you better responses in some of the models that you're using now, given the three or four, you know, prior doses and the exposure to natural infection?

Dr. Monto: An interesting question about dose finding. Do the manufacturers have any interest in replying? Jerry, do you?

Dr. Weir: No. I think you've probably seen everything with candidate vaccines that there is, but I'll turn it towards the manufacturers to see if they've evaluated something that they didn't present.

Dr. Monto: Pfizer.

Dr. Swanson: Hi. So early on in the evaluation of the original B and T 162 B2 vaccine, we did evaluate lower doses at the 10 microgram level in adults, and we did see nice increased response

going from 10 to 30 microgram. Now going into more of the variant adapted vaccine clinical experience, we've really focused on looking at whether 30 or moving up to 60 microgram, but not going down in the dose level because we're not seeing saturation going from the 30 to 60 micrograms. So it suggests that 30 microgram is a reasonable dose level.

Dr. Rubin: And that's fair. But, of course, the individuals now have seen a lot more doses of antigens. So it's not the same as when you did the initial studies where I do recall those data. I wonder if it would be the same now.

Dr. Swanson: Well, I think if we're moving toward more of a monovalent XBB, that will be much more of a new antigen component containing vaccines. So I think it would be in a good position to see reasonable responses with that composition.

Dr. Monto: Does Moderna want to reply? Yeah.

Dr. Das: Yeah. You know, we have worked to kind of keep the doses consistent to facilitate the licensure and kind of implementation across the populations. You're right. I mean, we have the 50 micrograms for the monovalent and a total 50 for the bivalent, which has the 25 of the XBB.1.5, and there we do see some benefit of the monovalent. Yeah. I don't know that I can comment on whether a lower dose of the monovalent would be further improved. I'm not sure.

Dr. Monto: And, Dr. Dubovsky, do you want to add to this?

Dr. Dubovsky: Yeah. In the early days, we did dose finding in the sera negatives, and there we found that a low dose, a five microgram dose, performed comparably to a 25 microgram dose. I think we're in different times now. Everyone's been exposed or vaccinated. And I draw experience more toward influenza where we know that higher doses in people who've been exposed many times actually do a better immune-response. And we presented some data recently for a higher dose formulation we're working on for older adults because we think this will, in

fact, lead to a better boosting regime. We have a very low dose vaccine right now with only five micrograms of antigen. And we have a lot of space we can go up to optimize the immuno-response. So that's something we're actively working on.

Dr. Monto: Thank you. Dr. Meissner.

Dr. Meissner: Thank you, Dr. Monto. I first want to echo the compliments to Dr. Weir. That was a fantastic overview of the issues that we've heard about today and in the past. So thanks so much for that. I also want to recognize the CDC for their genome surveillance because that has been so instrumental in helping us continue to think about the evolution of these mutant strains. So I just didn't want it to go unsaid how important that is. And I think the CDC is sequencing about 750 isolates a week, and I don't know if that's accurate, but I'd be interested. But then, Dr. Weir, I'd like to ask you, you mentioned that you compare the neutralizing titers or you validate the neutralizing titter assays among the different companies. And how well do they compare? Because they're likely different assays, and how similar are the results from those, number one? And then, number two, I'd like to ask about the duration of antibodies to XBB. We've been talking about different doses as a way of perhaps getting more antibody. Because the data that was shown only took us out a couple of weeks from the manufacturers. It was very helpful. But obviously time is limited. But is there any reason to think that there would be a longer duration of antibody to XBB, and especially to Novavax, with your matrix M adjuvant? Do you anticipate there might be a longer survival of or higher concentrations of antibodies?

Dr. Monto: Dr. Weir, would you care to speculate?

Dr. Weir: Yeah. Well, I can answer the first one and speculate on the second one.

Dr. Monto: Okay.

Dr. Weir: The first one is when I mentioned the assays, I don't think, and we don't really compare assays that one company sends in with assays for another. We certainly don't do studies that compare them. What we do is hold them to the same standards though, and we ask that they be qualified and validated, and we ask for the same sort of controls such that we can have confidence in the results. So it's not quite a comparative thing. And different companies use different types of assays. I mean, you hear a lot of pseudo virus type assays being mentioned, but every pseudo virus assay is not the same either. So we don't really compare them per se, but we hold them to the same high standards. And I will tell you that almost no one ever sends in an assay the first time that is perfect. They get lots of feedback from us, and we work with them so that we have confidence in their assays. That is important. And, again, I'm not trying to disparage studies that come from other places, but it is something that's out of our control when a study gets published in a pre-print with an assay that we have no idea of any details about. So anyway, I hope that helps with the assay question.

The second one is, as Dr. Monto said, will be a little bit of speculation on my part. I would guess, and I invite others to chime in, I would guess that the duration of antibodies with any variant will be somewhat similar to the duration of antibodies for some other variant. That being said, I think the higher the titer, even if the D duration is about the same, and call it a decay, it's not really quite a decay, but the diminution of the response goes down over time, if you start at a higher level, then you have something detectable for a longer period of time. So that would be my guess. And, again, that's part of the reason for trying to get a variant specific response that is higher for an XBB lineage virus than you have now. It's such that you will boost that titer up and hopefully it will stay at some level that contributes to protection for a longer period of time. But, again, I'm speculating. I'll let others chime in.

Dr. Monto: Dr. Dubovsky, would you care to speculate?

Dr. Dubovsky: Sure. So we do have a fair amount of experience with the adjuvant. And I agree, the higher you go, the longer it's going to be around. But what we've also observed is that we have an increased breadth of immune response. So as far as the small changes towards the variants, we seem to have really nice neutralizing responses that carry across all of those. So that may be one benefit of having an adjuvanted vaccine, not only against protection from the name strain, but also those from drift.

Dr. Monto: Dr. Das.

Dr. Das: Yes. So, you know, we do have some data about the durability for the BA.4/5. And I think the point is well taken about the question of the dose, as the slide is coming up, that the higher you start, the better. So that may be a reason against the dose ranging, but in this slide on the left panel, the pre boost titers are about eight months after receiving a BA.4/5 bivalent vaccine. And so you see, you have quite good durability for the BA.4/5 titers with the bivalent vaccine. But, you know, the durability of the titers versus the evolution of the variant is certainly hard to balance.

Dr. Monto: Thank you. Dr. Chatterjee.

Dr. Chatterjee: Yes. Thank you, Dr. Monto. My question is actually to either Dr. Weir or any of the manufacturers' representatives who are here. I just was thinking back to our discussion a year ago, and the recommendation at the time from the WHO was, if I recall correctly, to go with BA.1 as being one of the two components of the bivalent. And based on the data presented, we chose to go with the BA.4/5, along with the original strain. This time we're seeing a lot of data supporting the use of the monovalent BA.1.5, and I'm wondering if any of the

manufacturers or the FDA has any data on using more than one of these variants. So 1.5 and maybe 1.16 or 1.5 and 2.3. Has that been looked at by anybody?

Dr. Weir: I'll have to turn that to the manufacturer.

Dr. Monto: All right. Pfizer. And please raise your hands if you want to give some information.

Dr. Swanson: So thank you, Dr. Chatterjee, for the question. We did show data where we combined XBB.1.5 with the BA.4/5 of Omicron. We did not combine the 1.5 and the 1.16 in the preclinical studies, given how antigenically similar those two Omicrons were.

Dr. Chatterjee: Thank you.

Dr. Das: Yes, and we agree with that as well.

Dr. Chatterjee: Thank you very much.

Dr. Monto: Dr. Perlman.

Dr. Perlman: Yeah. So I have a question for the manufacturers. So we've been talking a lot about making the recommendations uniform and also about boosting, but one of the population of the zero to two year old children may be naive and they may not be, but for that group there's quite a disparity in the different recommendations from the different manufacturers. Is there going to be any effort to make the recommendations similar? So I believe now Pfizer recommends more shots than Moderna. I don't know what Novavax is doing, but is there any intent to try to make that more uniform across the different vaccine platforms?

Dr. Monto: Does Pfizer want to start?

Dr. Swanson: Actually, would FDA want to answer first and then I can follow up?

Dr. Monto: Dr. Weir?

Dr. Weir: I'm going to turn this one back to somebody in the common room. Dr. Kaslow. I mean, yes. Yes, there has been an effort for six months to simplify all of this. Over to you.

Dr. Monto: Yeah. This is not an easy question.

Dr. Kaslow: Yeah, no. This is Dave Kaslow. Yes. There's a whole effort to continue to simplify the immunization schedule. Probably first and foremost is a uniform age cutoff for children, transitioning from that multi-dose initial to a single dose thereafter. I think as you alluded to and related to that kind of first topic is reducing the complexity in that four to five years of age, in terms of dose and regimen and schedule. We are also, and I think it was touched on earlier, you know, reviewing the need in other populations for additional doses and lastly looking at schedules, individuals with certain kinds of immune compromise. So those are all under active consideration and will certainly be impacted by the decisions and recommendations that come out of this VRBPAC. So, yes, work in progress. Thank you.

Dr. Monto: Dr. Dubovsky, do you have something to add?

Dr. Dubovsky: Yeah, just to point out that we're authorized in the US in the age group of 12 and older. We're down in children as young as six months of age now, and we use exactly the same formulation as we use in adults, and it's tolerable in that age group. So as those studies conclude and we file for authorization approval in the US, I think we'll have a solution that'll be quite good for those kids.

Dr. Monto: And Pfizer?

Dr. Swanson: Yes. I think I just wanted to follow up. I think on your question more specifically on the pediatric population, and we do have ongoing studies evaluating the current bivalent BA.4/5 vaccine as both a two and three dose series. So we will have forthcoming data to

understand if in future the current primary three dose series for the youngest age group could transition to a two dose series.

Dr. Monto: Dr. Das, did you have something additional?

Dr. Das: Yes, please. So we do have the data for a bivalent vaccine as a primary series, as a two dose primary series, and we do support FDA's efforts certainly for harmonization. We've heard that this is a complex situation, particularly for children, and whatever we can do to simplify is important.

Dr. Monto: Okay. Thank you. It’s three o'clock Eastern. I see three hands raised from the committee Are these questions for either the manufacturers or Dr. Weir, because we have a long discussion ahead of us. Dr. Levy, is this a question?

Dr. Levy: Yes. Just briefly. I know our purpose here is to focus on the composition of the vaccine for the fall. You know, Dr. Offit brought up the topic of vaccine safety. We don't want to lose sight of that. We haven't heard a lot today about any updates regarding safety surveillance on the mRNA or Novavax vaccines from CDC or the sponsors. There's not time now to take a deep dive, but I'm wondering if they would comment because it's been a while since VRBPAC has met whether any new signals emerge or whether everything is more or less as we last left it in the realm of safety. Thank you.

Dr. Monto: That would be a question, I hope, for CDC because they can give an answer for all the vaccines.

Dr. Levy: Yes. Yes.

Dr. Monto: Because we don't need to go to each manufacturer.

Dr. Levy: Correct.

Dr. Monto: Let's park that and go back –

Dr. Marks: This is Peter Marks. I'm happy to respond.

Dr. Monto: Okay. All right.

Dr. Marks: Because I think it's actually a mutual question for CDC and FDA which share vaccine safety surveillance activities for the COVID-19 vaccines. So I think it's fair to say that there are no significant new safety signals that have been confirmed since the last updates presented to the committee. And, Dr. Kaslow, do you want to just confirm that my memory of that is correct? And perhaps if Dr. Forshee is listening, he could chime in.

Dr. Kaslow: Dr. Marks, that is correct.

Dr. Marks: Thanks very much.

Dr. Monto: Okay. Dr. McInnes, the last question.

Dr. McInnes: Thank you, Arnold. I have to say at this stage of development, I think we should be able to have seen those concentration curves with neutralizing antibody response for these vaccine candidates, and I don't guess I saw that. And I'm a little disappointed because I think we should. We know for sure with flu vaccines that you can continue to go up in HA concentration and continue to get an antibody response. And so we really didn't see any of those data, and there was some fumbling around about that. I'd like to know a little bit more about that in the next section. And then just one question. We've spoken that this is not flu, that we don’t know its seasonality, yet we're calling it a ’23-’24 vaccine decision, and I'm wondering if some other nomenclature is maybe more suitable for these candidates because it may not be a year. I mean, maybe we're going to be chasing this one. And so I'm just wondering about the nomenclature that has been selected. Thank you.

Dr. Monto: Dr. Weir, would you care to answer before we go on break?

Dr. Weir: Yeah. I mean, we can take that back and discuss if there's a better way to phrase it. But back to what you mentioned earlier, Dr. McInnes, about feeling locked in. I don't think you should feel locked in, in the sense that what we're doing is only locking in our course of action now for how to proceed. And if something changes in six months or four months or nine months, we will adjust to it, and we will come back to this committee. The manufacturers have shown that they're willing to respond, and I know you folks in the committee are, and so, yes, although we start now with the expectation that this is for 2023-'24, we will adjust as needed. Over.

Dr. McInnes: Thank you. Just one quick response to Jerry. I get it, Jerry. I know you'll do what we need to do. It sort of relates back to Bruce's comment about the word periodic and what that really means in this context of whether this is within a year. So I just am not sure that the nomenclature is helpful of what you're trying to achieve.

Dr. Weir: Okay. Point taken. I think the periodic, we use it and have used it to basically get across the fact that, what several of us have said, this is going to continue and we are going to do this. This won't be the last time we do this.

Dr. Monto: That's for sure. Thank you so much to everybody. Ten minute break. We come back at 3:15 for the discussion of the voting question. 3:15 Eastern.

Committee Discussion

Dr. Monto: We're now going to have a session where we will have discussion and voting. We usually have the vote as the end of the meeting after a long discussion. This time we're going to have some discussion about the voting question and then some further discussion about the topic of what lineage should be included in the vaccine if there is a yes on the voting question.

So, Dr. Weir, would you introduce the voting question, please.

Dr. Weir: I'll read it if someone will put it on the screen.

Dr. Monto: Yep.

Dr. Weir: Okay. So this is the question that we'll ask the committee to vote on after discussion. For the 2023-2024 formula of COVID-19 vaccines in the United States, does the committee recommend a periodic update of the current vaccine composition to a monovalent XBB lineage? Back to you.

Dr. Monto: And when you say periodic, you mean whenever is necessary, correct?

Dr. Weir: Yes, starting with right now for the next fall season.

Dr. Monto: Starting right now.

Dr. Weir: For the next fall season.

Dr. Monto: Right. As we go into the discussion, I would invite the members who we haven't heard from up to now to raise your hands and participate in the discussion. The way we should be going about this is to discuss whether we think there should be a change, if the change is indicated, should we be going to a monovalent vaccine, and if we are to go to a monovalent vaccine, is XBB lineage the appropriate one? We don't have to do those in sequence. That would be a little difficult. But we should be addressing all of those components because they are the components on which a yes vote will depend. Dr. Offit.

Dr. Offit: Yes. Thank you. Well, I certainly think that we should update this vaccine. I certainly think that Wuhan 1 no longer needs to be in this vaccine, and to include a currently circulating strain makes sense. The word periodic worries me. I'm not sure what is meant by that, and here's what I mean by this. I think some of the language that we've used today is going to confuse the American public, and I'll give two examples. One is the use of the term waning protection. I think we need to make it very clear what we mean by waning protection, because what we really mean is waning protection against severe disease. And in whom does that occur? This virus drifts, no doubt about it. And it drifts away from protection against mild disease. But it

does not drift away from protection against severe disease in people who are otherwise healthy and, say, less than 75. So I think that's number one.

Number two, we've used the word occasionally early on, and the word campaign was used. That implies sort of a yearly flu-like campaign. This gets to Ofer Levy's question earlier. There's abundant evidence on T-cells of both cytotoxic T-cells and T-helper cells from Alessandro Sette and Daniela Weiskopf and others at UCSD, as well as John Wherry at Penn. And recently, a paper out of Australia in immunity clearly shows the relationship between the activation and differentiation of helper T-cells and cytotoxic T-cells in prevention against severe disease, and the epitopes that are recognized by those cells are generally conserved. So the epidemiology is consistent with the immunology, which is that when Omicron came into this country and we saw a wave of infections, we didn't see as much of an increase in hospitalizations and death.

I'll take myself as an example, and then my rant is over, and you can ignore me. But I had three doses of Wuhan 1. In May 2022, I had a mild, two-day illness, probably with BA.2. So I was immunized with Wuhan 1. I got infected with BA.2 and had a mild, two-day illness. Now, that was a drifted virus. I mean, that's why I had a mild infection, but I didn't have a severe infection because presumably I had T-cells that prevented that severe infection, which may last for years. So I think we need to make sure that when we move forward here, I'm all up for updating this vaccine, but I think we need to define, and the CDC can help us with this, who really benefits from booster dosing because it's not everybody.

And the last fact, when we made this recommendation on June 28th last year, the CDC followed it up on September 1st by recommending that vaccine for everybody. And I think that wasn't the right recommendation. So I just hope that this becomes clear. This is not flu. Flu, you

know, is strain specific. We missed twice in the last 10 years on H3N2, and even if you got that vaccine and then you were exposed to H3N2, you had very little protection. That's not this virus. You still have protection against serious illness. I think we need to explain that to the American public because we're confusing them. Thanks. I'm done. Thanks, Arnold.

Dr. Monto: Okay. Next, Dr. Rubin.

Dr. Rubin: Thanks. And Dr. Offit is a tough act to follow, but I think what has been so helpful today is that there's been a consistent message from all of our discussions from the CDC, from the FDA, and from the manufacturers. And I think it makes it a pretty simple question here. The monovalent factor doesn't seem to be any particular advantage to a bivalent vaccine. XBB is the lineage right now, and there is good cross protection no matter what antigen is chosen according to the data that we've been shown. I think that the question of whether or not the word periodic should be in there is a reasonable question. However, I think that we need a better vaccine. We should be updating it, and I think it's pretty straightforward.

Dr. Monto: Thank you. Straightforward comment about a straightforward question. Dr. Lee.

Dr. Lee: Yes. I just wanted to clarify that all the data that we've been looking at so far, or most of it, has been on individuals who have already gotten the initial vaccine series, and in some cases an additional booster or maybe two boosters. Are we talking solely about boosters? Are we also talking about initial vaccines for those who have not gotten them? I'm thinking, in particular, there's been exceedingly low uptake among children under two. I think 90% are unvaccinated. Are we going to be recommending that for those who have not been vaccinated? I need some clarification on that. Thank you.

Dr. Monto: Thank you. Dr. Weir or Dr. Marks or Dr. Kaslow?

Dr. Weir: I can start real fast. The recommendation for the composition will apply to everything.

Dr. Lee: Okay.

Dr. Weir: Over to you, David or Peter.

Dr. Marks: Nothing further on my end.

Dr. Kaslow: That's correct.

Dr. Marks: I think it's one vaccine composition because we think it makes the most sense because it's actually circulating.

Dr. Monto: One size fits all.

Dr. Lee: Okay. Thank you.

Dr. Kaslow: Simplification.

Dr. Monto: Dr. Reinhart.

Dr. Reingold: That was close, Arnold, thanks. So, you know, I'm third or fourth in line here. I would strike the word periodic from this question. I think what we're being asked is do we think it should be updated for this fall? And I agree with Paul and others that we should. But, as worded, it seems to be saying, do we agree that there's going to be a regular need to update it? And I don't think that's clear. So I would change it to an update as opposed to a periodic update. Thank you. And I would also just say, when it comes to who should get this vaccine, that's up to ACIP basically.

Dr. Monto: Dr. Sawyer.

Dr. Sawyer: I agree that updating the vaccine with monovalent strain makes the most sense. I think the data is quite clear. I'll join the choir here. I think using the word season is equally problematic. It links the campaign to influenza vaccine, and I understand that it may be

convenient and most efficient to give the vaccines together, but, you know, it's only been a few years. We don't really know what the Covid season is, and it may ultimately confuse people about when and where they should get vaccinated and how frequently. I don't see that it gives us an advantage to predict what we're going to do beyond this fall, or I wouldn't even say this fall, beyond the time when a new vaccine can be produced. If that's next week, we should start giving it next week. So the other comment, I just want to follow up on Dr. Lee's comment and Dr. Reingold's presumption that the ACIP will discuss whether this vaccine should be given to everybody or whether it's going to be a subset.

Dr. Monto: Thank you. Dr. Cohn.

Dr. Cohn: Thanks. I will echo what's already been said. Oh, there you go. I'll echo what's already been said. I think I appreciate the straightforwardness of this question asking if we should be updating the current composition. Absolutely. To a monovalent? Yes, agree. We no longer need the Wuhan strain. And to this lineage, I would agree with that as well. I think I do want to be careful that we're clear that for this update it's monovalent. It may not be monovalent in future updates. And I do agree. I actually think the 2023 to 2024 formula language is more confusing than the periodic update. I think we're recommending an update. I think the language should be, do you recommend an update now? And whether or not that formula will carry through all of 2024, we can't really say. That's it.

Dr. Monto: Thank you. Dr. Marks, would you like to make a comment?

Dr. Marks: Yeah. I hate to be a contrarian, but, you know, from a public health perspective, people need to be able to understand what we're actually doing. And there's only so fast that our manufacturers can actually change things. So in order to make a few hundred million doses of vaccine, essentially, practically, we're going to have one update per year, barring a heroic effort

to deal with a strain that pops up that is essentially so different that it requires us to mobilize tremendous resources to address that strain change.

So for practical purposes, what we're talking about here, I think we can strike periodic, but for practical purposes so that the manufacturers can get on with this and actually label their vaccines, it's the 2023-2024 formula that they're making right now. And that's what's planned. That doesn't mean, just like for pandemic influenza, that something couldn't happen that could make us need to intercede here. And so I think I'm really having trouble understanding the committee's need to bristle against something that's similar to influenza.

People understand a yearly influenza vaccine at this point. It may not be yearly, but for all intents and purposes, it looks like probably by next fall there'll be further drift from this. And we may have to come back here. So I think this is our best effort to try to help make things clear. And I have to say we have to do better, because we have not done a good job to date communicating to the American public what's going on here, because they're still not getting these vaccines in the way we'd like to potentially see people, even those over the age of 65, get vaccinated. So this was our effort to try to clarify things. And, yes, I think periodic was just meant to mean that this is not going to be, what we end up with after today will not be the final. It's not like MMR. This is not going to be the final formulation for this vaccine forevermore. It will probably require another update at some point. Thanks very much.

Dr. Monto: Thank you. Dr. Bernstein.

Dr. Bernstein: Well, thank you, Dr. Monto. Coming after that statement, I actually, respectfully, don't agree with the discussion that Dr. Marks just said. It's not clear to me that this is a seasonal virus yet, and I do agree that it seems like all the stars are aligning for a monovalent vaccine rather than a bivalent product. It's not clear to me, thinking from a public health perspective, how

much complexity will be eased as we try to move forward with this, because I think implementation, who gets what and the number of doses and all and the communication in the public arena, will be incredibly challenging primarily for the ACIP, I believe. And so, for me, the word periodic is not a great term. And 2023-2024 formula suggests that this is going to be once a year. And I'm not sure, personally, that we're there with this virus that's not necessarily seasonal. And the last comment I'll make is I understood that these platforms that the manufacturers are using allow shorter timelines for production of vaccine. So, unlike flu vaccine, many made an egg or egg-based, I thought the turnaround for these were a shorter timeframe, which would allow appropriate changes as needed. Thanks.

Dr. Monto: As somebody who has been looking at the seasonal or common cold coronaviruses, they are sharply seasonal. And I think it's premature to say that this virus will not become seasonal once there is antibody in the population. So I agree we're not there yet, but we may be. And to say that it's not going to follow a familiar pattern may be premature as well. My two cents. Dr. Pergam.

Dr. Pergam: Thanks, Arnold. I'm not sure I have much to add to what my colleagues have said. I guess I'm really encouraged by the manufacturers, the FDA, even WHO working towards a similar idea of what would be in the updated monovalent. I think the data that is available looks as though it would be the right choice. I also like the idea that we'd have a global vaccine that would fit within not just the American public, but also worldwide. That would make this much easier for the companies to deliver and protect people around the world, which has been kind of a challenge up to this point. I guess I'm curious from the FDA's perspective, since there's all this discussion of periodicity, and I agree that the way this is worded related to the XBB lineage in the committee discussion question may not be the best way to word this. I'm curious whether the

FDA is thinking, similarly, whether the committee would get together on a, you know, a bi-yearly basis to review data and evaluate whether there would be an opportunity to update the vaccine similar to what WHO is doing and similar to how we do this on a yearly basis for flu.

Dr. Monto: Dr. Marks, do you want to comment?

Dr. Marks: Yeah. Well, you know, actually we don't do it on a yearly basis for flu at FDA. We actually do it twice yearly, because we actually also do it for the Southern Hemisphere. I think we agree with you completely that we would probably follow the WHO here and probably look at this twice yearly as well because it probably does make sense. And I think our sponsors would probably like us to do this as well, because I think Dr. Rye's (phonetic) point was very well taken that we need to think about not just the Northern Hemisphere, but the Southern Hemisphere middle latitudes as well.

Dr. Monto: Dr. Gellin.

Dr. Weir: Dr. Monto?

Dr. Monto: Yeah.

Dr. Weir: Can I make a quick comment? This is Jerry.

Dr. Monto: Yes, please.

Dr. Weir: I remind you that when we laid this out in the previous meetings, we agreed to do this at least once a year. And then we would obviously follow the science all year long, and we will clearly take this back and discuss whether it needs to be on some regularly scheduled basis or not. But, again, we said we would do it at least once a year at a minimum, and I think we all will continue to follow the science and follow the virus and see what's needed. Over.

Dr. Monto: Dr. Gellin.

Dr. Gellin: So wordsmithing by committee is never a good thing to do. So we shouldn't be doing that here, but I do think we do need to think about the words that we're using: campaign, booster, periodicity, up to date, fully vaccinated. What's a booster? There's been a lot of confusion. And maybe now that the pandemic is over, I think we can at least agree that they have been declared over, we can use that as an inflection point to try to think about our language going forward. There is or used to be, at the FDA, a Risk Communication Advisory Committee. It looks like they are paused for now, but somebody should take a look at the way we communicate all this stuff to make sure that we're sending the right messages and setting the right expectations. Thanks.

Dr. Monto: Dr. Levy.

Dr. Levy: Yes. Thank you. Can you hear me okay?

Dr. Monto: We sure can.

Dr. Levy: Okay.

Dr. Monto: We can’t see you.

Dr. Levy: You could see me now. Just getting my light on. So I think our discussion reflects the challenges of where we are now. We have safe and effective vaccines that are saving lives, we have some degree of public confusion, and we have a virus that continues to change and uncertainty about how often we're going to have to update the vaccine. And so, in that framework, I'd love to hear from FDA whether they continue to advocate with the other branches of our government regarding ongoing innovation in this space. Can we develop pan coronavirus vaccines? Can we develop vaccines that are adjuvanted and provide a longer and more durable and broader immunity? There are certain plans for ongoing clinical research. I'm not sure the commitment is still there on the preclinical end. And I'd love to hear from Peter Marks and others

how they view the bigger picture here. Because if we're in a pattern where we have to keep making changes, chasing variants, it's a difficult pattern.

Dr. Monto: Dr. Marks, do you wish to comment? It's not on the voting topic.

Dr. Marks: You know, I think if the question is do we think that we need a better generation of Covid? I mean, I think no one will disagree. And I certainly won't. Yeah. We need a better generation of vaccines that would offer a better breath duration, depth of protection. But I think we're here right now with what we have until we see that next generation come, which probably is at least two years away at the rate we're going.

Dr. Levy: Yeah. Thank you.

Dr. Marks: We have a bridge that we need. Is that what you meant? Yeah, I totally acknowledge this.

Dr. Monto: And, Dr. Levy, that's a cross government question as well.

Dr. Marks: Yeah. Well, and I think we're hoping that people will continue to work on these, and I think that there's been a fair amount of discussion around the government about trying to keep this moving through BARDA and their efforts and others because it's, I think, a critical thing that we try to move these forward.

Dr. Levy: Thank you. And that was as much for the US public. I mean, between us, I think we know these things, but I think there's a lot of, you know, people are tired of the pandemic. People feel like we have vaccines. We're done. But I think our discussion here reflects the challenges ahead and the need for further innovation. Thank you.

Dr. Monto: Dr. Sawyer. And I urge those who have not raised their hands to do so. We have a recycling of the same questioners, and some of our members have not been heard from.

Dr. Sawyer: I'll be very brief. I just want to raise another point about the confusion the language may create. It'll depend on what ACIP recommends, but the use of seasonality and campaign automatically links this vaccine to influenza because that's the only virus for which we have a seasonal campaign at the moment, RSV pending. And so I do think if ACIP were to recommend this vaccine only for a subset of the population, and we're using this word campaign to talk about something, influenza that everybody gets is going to create confusion. And vice versa could happen if a subset of the population is recommended to get Covid vaccine. That same subset or those not in that subset may assume they no longer need influenza vaccine. So I think the language is important.

Dr. Monto: Dr. Chatterjee.

Dr. Chatterjee: Thank you, Dr. Monto. I thought I might try to offer a friendly amendment to the language of the voting question, if that is allowed, to say something like, for the 2023, no mention of 2024, for the 2023 version of COVID-19 vaccines in the US, does the committee recommend an update of the current vaccine composition to a monovalent XBB lineage. I believe that would take out some of the language that is troubling to my fellow committee members. And I'd just like to point out there's been, yes, a number of people have mentioned seasonality and campaigns and things, but those words do not appear in the current version of the wording question. So it is important, I think, to communicate clearly and better with the public at large to explain exactly what we are talking about here. But I believe that if we change the wording in the way that I suggested, that might take away some of the concerns that have been raised.

Dr. Monto: Dr. Marks.

Dr. Marks: Sorry. I would respectfully say that we will be stuck with this for 2023-2024 because the manufacturers will, as Novavax has said, if we decided, for instance, now even that we were going to change the composition, this vaccine will be used into 2024. So with all due respect, I think we are selecting something that will be used in 2023-2024. And for reasons that have to do with how we've worked with the manufacturers, I think we're selecting something that, barring some new major development that requires agile public health response, we're dealing with a vaccine that will be used from 2023 in through to 2024 for practical purposes.

I very well take the point here that we don't want to talk about seasonality, that we don't want to talk about periodic, but for practical purposes, this is the vaccine composition for 20. I mean, if we want to say do we believe in a monovalent XBB vaccine for the 2023-2024 vaccine composition, leaving aside periodic and leaving aside anything else, I think I can certainly live with that. But I think, for practical purposes, it's 2023-2024. And I'll turn it over to Dr. Kaslow to see if he has any. I'm happy if you disagree, David, but let's just try to make sure we're on the same page on this.

Dr. Kaslow: Okay. I'm just wondering if we're all conceptually on the same page, and we're dealing with, you know, word details and that sort of thing. I think what we'd really like to hear is, conceptually, are we all on the same page, which is, first, we need a periodic update. Second, it's time to move from the current bivalent to monovalent. Yes, we may need to move to a bivalent in the future if the evidence suggests that, but the evidence today suggests that it's a monovalent, and that monovalent should probably be in the XBB lineage. And to Dr. Marks's point, the opportunity to change this again in 2023 or early 2024, I think, is remote.

Dr. Monto: Remote, but possible if there are dramatic developments?

Dr. Kaslow: That is correct.

Dr. Marks: Okay. I mean, I think we have commitment from the government to, obviously, mobilize just like we would for influenza. We would mobilize and move in dramatic measure if a variant appears that escapes the ability of our current protection, in other words, starts to cause mortality in young individuals who have been previously immunized or previously had COVID-19, in other words, an escape variant. I think we would mobilize to try to get something, regardless of when it would be, as quickly as possible. But, for practical purposes, you know, as fast as it can be done, it's probably a 90 to 100 lag between when we see that variant and mobilize to do so and when we'd actually have it. So even just for practical purposes, you can see that this current selection will likely take us into the new year, and hopefully we won't have something appear in the next two or three months that will require us to scramble.

Dr. Monto: Thank you. Dr. Wharton.

Dr. Wharton: Thank you. I just wanted to support the voting question. I think moving to a monovalent is a good idea at this point. There's no reason to continue using the Wuhan strain, and I think the evidence is good that this currently circulating XBB is the correct strain to use.

Dr. Monto: Thank you. And let's follow Dr. Wharton's example and stick to the discussion of the voting question. Dr. Hildreth.

Dr. Hildreth: Thank you, Dr. Monto. I agree with moving to monovalent XBB, that lineage vaccine, but I'm also concerned that we remove any barriers to people choosing to use the Novavax vaccine. I think there's great value in a heterogeneous approach to vaccination. So even those who've gotten the mRNA vaccine should have access to the Novavax if they choose to do so, as I would, if I have ability to do that.

And I know what you just said, but I do want to mention the fact that now that the public health emergency has been declared over, I want to make sure that there's a provision made for

those who don't have medical insurance to actually have access to the vaccines. Because if they don't have access, then we can't have the public health benefit that we are all hoping for here. So those are my comments. Thank you.

Dr. Monto: Thank you. Very important comments. Dr. Berger.

Dr. Berger: Thanks. I will try and make my comments very specific to the three questions you asked, Arnold, and I do have a question for FDA after that. So should there be a change? Clearly the data suggests that the old variants are no longer circulating. XBB is. So, yes, it makes sense. Should it be monovalent? It seems like that gives us a good response, and there doesn't seem to be an advantage over the bivalent. So, yes, I do think it should be monovalent. And your last question is should it be XBB? As I said at the beginning, yes.

I do have a question for FDA along these lines though, especially in terms of the transparency that, Peter, you were saying, I think the data that we've seen so far, at least, presented suggests that the current vaccine actually is no longer detecting the current circulating viruses. And I'm wondering if FDA plans to, you know, say anything about the currently available vaccines before this, and I'll use the term knowledge of the tier, which is the 2023-2024 formulation, that will consist presumably of the monovalent XBB lineage?

Dr. Monto: Question for FDA.

Dr. Marks: This is Peter. I just want to make sure, what you're saying is given the decreased effectiveness of the current vaccines relative to what we expect from this new generation, would we make some statement at this point?

Dr. Berger: Yes. That's exactly.

Dr. Monto: In other words, because the vaccine is still available and being administered, the bivalent.

Dr. Berger: Correct.

Dr. Marks: You know, let me just ask David, Dr. Kaslow, if you'd like to comment on this, and then I can comment on it.

Dr. Kaslow: I mean, currently what we have available are three authorized vaccines of which are bivalent, one of which is the original, which is the original monovalent. And back in April, we took a look at, as part of the consolidation, the available evidence. And at that time demonstrated that that bivalent across all ages and all doses provided a favorable benefit risk.

Dr. Marks: I think the way we would say this is that in the absence of having these updated vaccines versus nothing, in an older age group, this does provide some benefit. Right? I do think we will have to have some conversation with our colleagues at CDC because, at a certain point as these become available, we probably want to make it clear to providers that it's not advisable to give additional boosters prior to wanting to give one of these updated vaccines. So I think that point is well taken, if that's what, I think that might have been implicit in that question. And that point is well taken, and we can take that back to discuss with our CDC colleagues.

Dr. Berger: Yeah, that’s where I was getting at, so thank you.

Dr. Marks: Got it. Got it. So that point, thank you. That point's very well taken.

Dr. Monto: That's an important point.

Dr. Marks: Yes, because we would agree that probably sometime in the next month or two, people should stop, even if they were considering. So totally agree. And we can take that back for a discussion.

Dr. Monto: Thank you for raising that because that is going to depend, as well, on the amount of time you have to wait to get the new booster.

Dr. Berger: Yeah. And we also heard, and I can't remember which manufacturer this was, they may even have theirs available, if it is the XBB.1.5, it could be as available as soon as July. So we aren't talking far off into the future

Dr. Marks: Point well taken. Thanks.

Dr. Monto: Thank you. Okay, Dr. Nelson.

Dr. Nelson: Thank you, Dr. Monto. I commented earlier, but I'd want to go back to the four key question frame work to address this question that Jerry Weir so eloquently outlined at the beginning of his remarks. So for me, yes, to new circulating variants being antigenically distinct. Yes, to new variants being dominant. Yes, data supports current vaccine is losing efficacy against emerging variants. And, yes, thanks to industry and our manufacturing presenters today for conducting that at-risk manufacturing in the studies that we now have data supporting better efficacy with the candidate vaccines under discussion.

To address the monovalent issue in the question, agree that for this year, given the consequence of immune imprinting with inclusion of legacy strains for this year, it does make perfect sense to move towards a monovalent vaccine. Whether that holds up for future years, I don't think we know at this point. Addressing the periodic issue, I get the intent of the question. So, overall, yes, no matter whether you change it or not, that's probably how, that will be how I'll be voting. I support periodic assessment and updating on a schedule to be determined in a generic fashion, and certainly acknowledge and really don't have a whole lot of heartburn over annual planning factors, so once yearly expecting to revise this vaccine due to practicality purposes, but also because the neutralization data that's been presented, it shows that cross reactivity does occur, and it doesn't drift that much faster than over a single year.

And I too am not ready to submit that this fire should be considered an exclusively fall or seasonal virus. And, as I've said in the past, I don't think we should provide any language or communication that restricts its administration of the typical flu season. We currently have biphasic, summer, and fall peaks. Yes, they're smaller than they have been previously, but that summer peak is not going away. And I'm not sure we fully understand the risk of peak shifts as the population gets further away from their current primary boost primary series and their booster doses, as well as their natural infections. Plus, we don't know what's going to happen to individuals who get a summertime infection, for example. Are they really going to be protected for the entire next year? So, for those reasons, there's certainly a lot of work to be done with the periodic question, but the main answer to the question on the table is yes.

Dr. Monto: Thank you. Dr. Hawkins.

Dr. Hawkins: Well, thank you very much, Dr. Monto. So I agree with the update. As we know, persons are still dying of Covid or are having severe illness. We also have a substantial number of people who are vaccinated, who are having mild to moderate symptoms. I had four or five in the last two weeks. I believe that the FDA remains committed to surveillance, evaluating the science, and I believe they will be as agile as possible, something that Dr. Marks mentioned a couple of statements back. So I have categories of patients who they were never vaccinated. They still won't take the vaccine despite what their losses are. We have a bunch of folks in my practice and in the community who will say, yes, give it to me as long as it's safe, and the vaccinated is safe. But we have a substantial number of maybes, folks who say, Well, I'm not sure, Doc, what do you think? And so that's what the public is asking of us now.

And I think that although we think about folks with mild symptoms, I want to remind us all that some of these folks with mild symptoms have really significant comorbidities, and they

exacerbate, they get hospitalized. And although they may be counted as a Covid related death, they are losses too. So I think that we should, and I get the sense that we all agree, but I think that we need to be definitive in supporting this and perhaps not get caught up so much into the weeds of every word or every other word. Thank you.

Dr. Monto: Thank you. Dr. Meissner.

Dr. Meissner: Thank you, Dr. Monto. Two comments. First of all, Dr. Levy raised an important point, but, as Dr. Marks said, BARDA is laser focused on next generation vaccine and spending an enormous amount of time and effort on what we can do to improve the current generation of vaccines. Secondly, I think that the reluctance among many people at this stage to get the vaccine is based on the reducing rates of severe disease, and that's what's going to drive uptake of this vaccine. And I agree with making a monovalent XBB sublineage, but that's what's going to drive uptake. If this virus continues to decline in disease severity and in rates and approaches the four seasonal coronaviruses, then it's going to be difficult to convince many people to get this vaccine. So I think that also has to be factored into the language that comes from the CDC. It has to be realistically aligned with hospitalizations and severe disease and death. Thank you.

Dr. Monto: Thank you, Dr. Meissner. Dr. McInnes.

Dr. McInnes: Thank you, Arnold. I support the recommendation of an update to the monovalent XBB. I don't like the periodic there. I think it's confusing to issues. I think this is a recommendation for an update. The second point is that periodic updates of available data for future strain changes should be continued. So I think these are two thoughts. I think that second sentence isn't necessary. It's what you do all the time if you want it there, but I don't like a periodic update to a monovalent XBB lineage. I don't think it makes sense. Thank you.

Dr. Monto: Thank you. Dr. Kim.

Dr. Kim: Well, thank you. I'm a part of the unanimity of this committee in thinking that the monovalent XBB lineage update is necessary, given the evidence that's been presented to us today. But perhaps as a minority on the use of 2023 or 2024 and possibly the use of the term periodic, you know, it wasn't that long ago that we were actually talking and talking about the pandemic and discussing the need to try to get ahead of the curve given what we know about coronavirus, given what we know about its seasonality, and given what we know about influenza and the impact that these diseases will have together on the American public.

And we were talking about how to leverage the system, the infrastructure that we currently have, with the influenza vaccination efforts to try to promote the uptake of the Covid vaccine. And I really don't want us to lose track of that and the fact that we can use what we currently have. We can make all these recommendations, but if the system isn't set up to promote the uptake, then I think the recommendations are limited. So I actually am in favor of using some of the language that we are using for influenza to see about adding more oomph to the campaign to promote the update of the Covid vaccine along the lines of influenza vaccine and anything else that we might deem necessary, based on what we currently know, not necessarily based on what we expect to happen or hope to happen or the things that might happen down the line. So I think we really do need to try to be consistent with our messaging, and that has been our message in the last two, three years.

Dr. Monto: Thank you, Dr. Kim. And, Dr. Perlman, last question before we vote. No additional hands raised. Voting is going to come.

Dr. Perlman: Yeah. So I just wanted to comment because I agree with both the input or the goal of this question and also some of the caveats that have been raised by the committee. I think that one thing I'd like to just agree with even more is the comments that Dr. Offit and Dr. Meissner

made about who should get this vaccine because this is part of the messaging. And in the rest of the world, I believe, I didn't hear Dr. Subbarao talk about this, but I believe even the WHO said that only select populations should get the vaccine. And so we have to deal, I think, with the worldwide situation and the fact that so few people are getting boosted with the bivalent vaccine. So I think the messaging that the FDA and the CDC do together is really critical in moving forward. If this virus keeps circulating to high levels, it may well be that people are boosted all the time and that the need for a vaccine will be less apparent for those people, not for everybody. But, anyway, that's all.

Dr. Monto: Thank you, Dr. Perlman. So now can we pull up the voting question so I can read it?

Dr. Marks: Dr. Monto, this is Peter Marks.

Dr. Monto: Yep.

Dr. Marks: I think we can certainly make one change to this to try to make it a little bit simpler for people who may be having heartburn. Not that I want to deny the makers of calcium carbonate products some takers, but maybe we could remove the word periodic there. Just recommend an update of the current vaccine composition and that way some people might just feel better about this. Point taken

Dr. Monto: It really is unnecessary.

Dr. Marks: Right.

Dr. Monto: Okay.

Voting Question

Dr. Paydar: Dr. Monto, if you would be kind, let me read my statement, and then we will have you read the voting question. Does that make sense? So we have 10 regular members, and 11 temporary voting members. A total of 21 will be voting in today's meeting. As you can see, the

names on the slide. With regards to the voting process, Dr. Monto will read the voting question for the record, and afterwards the AV staff will move all non-voting members and FDA staff out of the main room. Only the voting members and the DFOs will be in the main voting room. For those non-voting members, please do not log out of the Zoom. We will be with you after the voting has concluded.

Once all non-voting members are moved out of the main room, all regular voting members and temporary voting members will be shown the polling part on their screens, and I'll ask that they cast your votes by selecting one of the three voting options, which includes yes, no, or abstain. You'll have one minute to cast your vote after the question is read. Please note that once you have cast your vote, you'll 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 of the votes have been tallied, we'll broadcast the results and read the individual votes aloud for the public record. Does anyone have any questions related to the voting question before we begin?

If not, Dr. Monto, if you would be kind to please read the voting question for the record.

Vote Results

Dr. Monto: Okay. Are you going to put it up? There it is. Okay. For the 2023-2024 formula of COVID-19 vaccines in the US, does the committee recommend an update, no word periodic, an update of the current vaccine composition to a monovalent XBB lineage? Yes, no, or abstain.

Dr. Paydar: Great. Thank you. At this point, I ask the AV team, please go ahead and move all non-voting members out of the main room. Please don't log out of the Zoom. We'll be with you in few minutes.

Thank you. There are 21 total voting members for today's meeting. The vote is unanimous. We have 21 out of 21 yes votes. Here are the voting responses for each voting

member. I'll read them aloud for the public record. Dr. Archana Chatterjee, yes. Dr. Mark Sawyer, yes. Dr. Amanda Cohn, yes. Dr. Steven Pergam, yes. Dr. Michael Nelson, yes. Dr. Paul Offit, yes. Dr. Eric Rubin, yes. Dr. Jeannette Lee, yes. Dr. Arnold Monto, yes. Dr. Arthur Reingold, yes. Dr. Cody Meissner, yes. Dr. Bruce Gellin, yes. Dr. Adam Berger, yes. Dr. Stanley Perlman, yes. Dr. James Hildreth, yes. Dr. Melinda Wharton, yes. Dr. Randy Hawkins, yes. Dr. Ofer Levy, yes. Dr. Henry Bernstein, yes. Dr. David Kim, yes. Dr. Pamela McInnes, yes.

This concludes the voting portion for today's meeting. I'll now hand over the meeting back to Dr. Monto for the committee for the vote explanation and discussion topic. Thank you so much. Dr. Monto.

Dr. Monto: Thank you. And if any of the committee wishes to explain their vote, please raise your hands. I'm not going to go around and call on everybody because we have the discussion topic to get to yet, which is going to require some of our time. So if you'd like to explain your vote, please raise your hand. Dr. Cohn.

Dr. Cohn: Thanks. I think, as you can see by the vote, this was really very well presented and very straightforward in terms of the data informing this particular question around the actual composition of this vaccine. I do just want to say that I really appreciate FDA and Dr. Marks's explanation around this expectation that we should only anticipate a strain change under normal circumstances once a year. I think that actually helps frame this better in the future, and I hope that we can get to a place where there's at least a regularly scheduled knowing in advance when you're going to review the data with the committee so we can get in a regular routine of looking at this. Thank you.

Committee Discussion of Vaccine Strain Selection

Dr. Monto: Thank you. Now let's move to the discussion topic. Dr. Weir, would you like to introduce that?

Dr. Weir: I can if someone will flash it up.

Dr. Monto: Yes.

Dr. Weir: I can read it.

Dr. Monto: And give us some guidance.

Dr. Weir: Oh, okay. I don’t know about the guidance part.

Dr. Monto: There are three variants mentioned that we haven’t even hear much about one of them.

Dr. Weir: Okay. Based on the evidence and other considerations presented, please discuss selection of a specific XBB lineage, for example, XBB.1.5, XBB.1.16, or XBB.2.3, for inclusion in the 2023-2024 formula of COVID-19 vaccines in the US. I don't have much guidance. You've heard everything there is to hear about the data available among these three subvariants of the XBB family, for lack of a better word. I think it's fair to say it's not an easy choice. It may not even matter, but that's what we want to hear the committee discuss based on what they heard from a decent amount of data from the manufacturers, from their preclinical studies, and one clinical study. Other than that, no other guidance from me, but we appreciate your input and thoughts. Over.

Dr. Monto: For guidance, what if we decide that we don't have sufficient information to make a recommendation? What will you do then?

Dr. Weir: You can say that, and that's fine because you've already made a recommendation that the vaccine should be monovalent and XBB. You can make any comment or recommendation you want. We will take that into consideration and huddle again and see what we can, the best we can come up with to talk to the manufacturers.

Dr. Monto: My final question. Do you envision a situation where one manufacturer may choose one variant and another manufacturer choose another? Or do you wish all of the manufacturers to use the same variant?

Dr. Weir: I wish they would all use the same, and before today, I would've said that's more of a possibility than after what I've heard today. But, again, I guess any of this could happen.

Dr. Monto: Dr. Marks.

Dr. Marks: Yeah. No. Ideally, we'd like to have the composition be similar, and I think it's not unreasonable, in order to guide the discussion at this hour, I think what you heard from the manufacturers is that XBB.1.5 looks like it seems to be at the front of the line because of some of what is available in terms of its manufacturing and its properties. So it might be helpful to hear a discussion of anyone who thinks that we should consider the other variants instead. Because I think if everyone, just by way of full transparency, if everyone says that there's no preference in the committee, my guess is that, although I can't say for sure, but my guess is we would go back and go towards XBB.1.5.

So it might be good to hear discussion of any thoughts for things other than 1.5, in part because that would allow the composition to be similar for all of the vaccines to be made available in a very timely manner and because the data seemed to show that particular variant seems to have very good neutralization across this group of XBB variants, including 2.3. Over.

Dr. Monto: Thank you. That's exactly what I was hoping you would say. Dr. Rubin.

Dr. Rubin: Well, there's not that much to add to that. The data we've been presented with show us really no difference among any of these. And these are reassuring, in fact, that there is a lot of cross neutralization for, at least in the animal models, for 1.5 and 1.16, and in the small number of patients who've gotten them. Given that, it's a practical question. The manufacturers

have already been working with 1.5 and in some cases 1.16, and the WHO has given a sort of iffy endorsement of either one. It seems like we should just follow up, go practically and whatever is simplest and best aligned.

Dr. Monto: Thank you. Dr. Pergam.

Dr. Pergam: Yeah. I tend to agree. I think, you know, it sounds like we would like to have a similar approach in terms of the worldwide, you know, vaccine component if possible. I think we're in a different situation than we were last time when we were talking about, you know, BA.1 versus BA.4/5, where we actually had some data that suggested that BA.4/5 might be a better choice, and we made that decision based on early data.

I don't think it seems as though the XBB viruses are that much different. My only question, and I think this is important, is if the vaccine is available and manufacturers can get it out, let's say at the end of July, when would be the time that we would make this available for the public, knowing that there is waning of immunity, if we're thinking of, again, if we're going to put coronavirus or SARS-CoV-2 in a seasonality and look for a fall/winter season, what would be the timing of when we would roll this out? I think that is the question that would be important to be thinking about. That’s not up to us. It's up to ACIP and others, but I think it’s going to be an important decision.

Dr. Monto: It's a very important question, but the problem is I don't know that there's a very clear answer.

Dr. Marks: I think the best I can suspect, and I'll ask Dr. Kaslow to comment, is given there's the manufacturing issues and then there's the supply issues and other regulatory issues, my guess is we're looking at something in the September timeframe for seeing a rollout, but don't hold me exactly to it. But I think September-ish sounds correct.

Dr. Kaslow, thoughts?

Dr. Kaslow: Yep. I agree with you, Dr. Marks. And to get back to an earlier conversation, and there's other evidence gaps that need to be filled in order to get these approved, and some of them may still be in the authorized versus approved status, so, September sounds right.

Dr. Marks: I'm sorry. Just so you know that our short term recall is intact, I think, from Dr. Pergam's question, that does mean that we will recognize that in the not too distant future we have to work with our CDC colleagues to make some statement about whether people should continue to further get the current vaccine. So we'll take that back. So don't worry. That is on the list. Thank you.

Dr. Pergam: Thanks.

Dr. Monto: Dr. Wharton.

Dr. Wharton: Thank you. What we've seen suggests that there's not much difference in terms of the immune response with these three specific lineages. The 1.5 looks good. It seems like it's the most feasible to get across the finish line early without resulting in delays in availability. And the vaccine we can use is the vaccine that we can get. And so it feels like this would be a good choice, and it's great that we've actually been able to see as much information today about it as we've been able to see, including the one clinical study. So thanks to everybody for providing a pretty robust body of data for review today.

Dr. Monto: Dr. Sawyer.

Dr. Sawyer: Putting aside the discussion of seasonality and periodicity and campaigns, we all expect this infection to come back in the wintertime, so I agree with Dr. Hildreth's comments that it's important that people have the choice and that we have as many vaccines as possible. Given the timeline for the Novavax product, I would argue that we should at least include 1.5

among the recommended strains, because that's the one they've already started producing. I'm indifferent as to whether we allow the other manufacturers to use 1.16 or 2.3.

Dr. Monto: Thank you. Dr. Gellin.

Dr. Gellin: Yeah, echoing through what Peter was saying, I think consistency is a good thing. I mean, I was glad Jerry gave us the language from the other regulatory bodies. We might want to look at some of those because, for the most part, they implied flexibility. So I think, as Dr. Rubin was saying, I think it is a practical one for which one of these work best in the hands of the manufacturers. But I'd also want to make sure a couple things, that there are systems in place down the road to actually evaluate, if there are differences, what we might learn from them during the season. And, as far as labeling, you hate to have people say, Well, I got 1.16 and you got this. So somehow we should signal that these are interchangeable, whatever the right word is, so that these are seen as equivalent. Thanks.

Dr. Monto: Dr. Nelson.

Dr. Nelson: Thank you, Dr. Monto. I would throw in my support for 1.5. Rationale for it, first, we heard data today that 1.5 is the best immunogen overall of the three under consideration. There's good cross neutralization data is number two. Number three, inferring from the presentations, the three manufacturers clearly are preferred to proceed with this particular variant and can make it available, which improves accessibility. Number four, given that we are committed to making evidence-based decisions, overall the greatest data is indeed available for 1.5 and not some of the newer variants that are on the table. And then the fifth one is this issue of harmonization both globally and nationally. So thank you.

Dr. Monto: Dr. Levy.

Dr. Levy: I would agree with my other colleagues that the XBB.1.5 makes sense for the reasons stated. As we look to the future to improve our processes, whether investments in approaches at forecasting, trajectories of new variants, machine learning coaches, that's something we should look at as an area to improve so that in the future we get at forecasting. Thank you.

Dr. Monto: Thank you. Dr. Perlman.

Dr. Perlman: Yeah, so I agree with that recommendation too. I think one point is that we may, well, in the next month find that XBB.1.16 or XBB.2.3 become more dominant than XBB.1.5, and this doesn't matter, though, because I think we have good data that there's really good cross reactivity within the S protein and that other parts of the virus may matter. So as we communicate this, we should make it clear that, even though the name changes for the S protein, there's not that many changes. So this should work just fine.

Dr. Monto: Thank you. So in summary, we, in general, feel that XBB.1.5 would be preferred. We don't have any strong feelings about using other variants. But the fact that most of the manufacturers are ready to work on an XBB.1.5 is an added reason to select this strain or this variant given the immunologic data. And we've always made the point that we're not chasing variants. And even if other variants in this XBB lineage become more prominent, the XBB.1.5 seems to elicit appropriate antibodies. And I think that is a wrap in terms of our meeting.

I'll turn the floor over to the Director, who I think is going to make some closing comments.

Closing Comments — Dr. Peter Marks

Dr. Marks: Thanks. Thanks, Dr. Monto. First of all, let me just thank people for a minute. I want to thank all of the advisory committee members for a really good discussion. I really appreciate the input, and I think we're very sensitive here to making sure we try to do our best to

get it right, to get the most people who should be vaccinated, vaccinated, and to have the most confidence in those vaccines that are deployed. And we'll do that working with our CDC partners. So we'll look forward to that. We really appreciate the input.

I want to also thank the presenters today from CDC, WHO, and our Open Public Hearing participants, as well as a real thanks to our advisory committee staff and our AV staff who have really pulled this off. It's really wonderful to have these meetings really work nicely and flawlessly, as they did today. So thank you so much for that. And, finally, I just want to say that, you know, what we heard today is that we did hear the recommendation for an updated composition to an XBB containing monovalent vaccine. We did hear the preference for an XBB.1.5 vaccine. And we'll make a decision quickly regarding the specific composition to recommend to manufacturers for the coming season.

I think our decision obviously will incorporate what we've heard today. And I don't think it will come as any surprise based on the discussion today. And then we anticipate that the manufacturers will be moving forward with manufacturing and then obtaining data and filings needed to inform our ultimate FDA actions, in order to have vaccines evaluated with our safety and effectiveness standards for availability in the September timeframe. So really want to appreciate all of the feedback. And I did forget one group. I want to thank the sponsors for really doing a wonderful job providing the information which really helped us come to this as easily as I think we were able to today. So thank you everyone, and really appreciate everyone's effort here.

Adjournment

Dr. Paydar: Thank you, Dr. Marks. I also wanted to thank the committee and CBER staff for working so hard to make this meeting a productive meeting. I now call the meeting officially adjourned at 4:27 PM Eastern Time. Have a wonderful evening everyone.