Food and Drug Administration (FDA)

Center for Biologics Evaluation and Research (CBER)

185th Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting

Zoom Video Conference

June 5, 2024

*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

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**Acting Chair**

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**Members**

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| Adam C. Berger, Ph.D. | Director, Division of Clinical and Healthcare Research Policy Office of Science Policy Office of the Director National Institutes of Health | Bethesda, MD |
| Henry H. Bernstein, D.O., MHCM, FAAP | Professor of Pediatrics Zucker School f Medicine at Hofstra/Northwell Department of Pediatrics Cohen Children's Medical Center | 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 |
| Hayley Gans, M.D. | Clinical Professor, Pediatrics-Infectious Diseases Stanford Medicine Children's Health | Stanford, CA |
| CAPT Sarah Meyer, M.D., M.P.H. | Chief Medical Officer, Immunization Services Division National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention | Atlanta, GA |
| Paul Offit, M.D. | Professor of Pediatrics Division of Infectious Diseases Children's Hospital of Philadelphia, Maurice R. Hilleman Professor of Vaccinology Perelman School of Medicine, University of Pennsylvania | Philadelphia, PA |
| Stanley Perlman, M.D., Ph.D. | Professor, University of Iowa, Distinguished Chair Department of Microbiology and Immunology, Carver College of Medicine, University of Iowa | Iowa City, IA |

**Temporary Voting Members**

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| Bruce Gellin, M.D., M.PH. | Chief, Global Public Health Strategy The Rockefeller Foundation | Washington, DC |
| Jeannette Yen Lee, Ph.D. | Professor of Biostatistics, University of Arkansas for Medical Sciences | Little Rock, AR |
| Ofer Levy, M.D., Ph.D. | Staff Physician & Principal Investigator, Director, Precision Vaccines Program Division of Infectious Diseases, Boston Children's Hospital Professor, Harvard Medical School Associate Member Broad Institute, Massachusetts Institute of Technology | Cambridge, MA |
| H. Cody Meissner, M.D. | Professor of Pediatrics and Medicine at Geisel School of Medicine, Division of Infectious Diseases | Hanover, NH |

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| | and International Health, Dartmouth-Hitchcock Medical Center | |
| Michael Nelson, M.D., Ph.D. | Professor of Medicine Chief, Asthma, Allergy, and Immunology Division UVA Health & UVA School of Medicine | Charlottesville, VA |
| Mark Sawyer, M.D., FAAP | Professor of Clinical Pediatrics Division of Infectious Diseases Vice Chair for Education Department of Pediatrics University of California San Diego School of Medicine, Director, UC San Diego Pediatrics Residency Program, Rady Children's Hospital San Diego | La Jolla, CA |
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| Robert S. Janssen, M.D. | Chief Medical Officer, Senior Vice President Clinical Development, Dynavax Technologies Corporation | Emeryville, CA |
| **Acting Consumer Representative** | | |
| Randy Hawkins, M.D. | Physician, Pulmonary and Internal Medicine Private Practice | Inglewood, CA |
| **Speaker** | | |
| Ruth Link-Gelles, Ph.D., M.P.H. | CDR, U.S. Public Health, Service, Vaccine Effectiveness Program, Lead Coronavirus and Other Respiratory Viruses Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention | Atlanta, GA |
| Natalie Thornburg, Ph.D. | Acting Chief Laboratory Branch Coronaviruses and Other Respiratory Viruses Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention | Atlanta, GA |
| David Wentworth, Ph.D. | Technical Advisory Group on Coronavirus Vaccines World Health Organization (WHO) | Geneva, Switzerland |
| **Industry Speakers** | | |
| Kayvon Modjarrad, M.D., Ph.D. | Executive Director, COVID-19 Program Lead Moderna, Inc. | Cambridge, MA |
| Kayvon Modjarrad, M.D., Ph.D. | Executive Director, Viral Vaccines & Immunology Vaccine Research and Development Pfizer, Inc. | Pearl River, NY |
| Frances Priddy, M.D., M.P.H. | Executive Director, Clinical Development, COVID-19 Vaccines Moderna, Inc. | Cambridge, MA |
| Robert Walker, M.D. | Senior Vice President Chief Medical Officer Novavax | Gaithersburg, MD |
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## Opening Remarks: Call to Order and Welcome

Dr. Monto: Good morning. This is Arnold Monto at the University of Michigan in Ann Arbor. I would like to welcome you all to the 185th meeting of the Vaccines and Related Biological Products Advisory Committee of the Center for Biologic Evaluation Research of the FDA. Today we meet in open session to discuss and make recommendations on the selection of the 2024-2025 formula for COVID-19 vaccines. The members and voting, member, acting members are reminded to turn on your cameras and your microphones when you are recognized to speak.

First, I'd like to give over to Kathleen Hayes, the designated federal officer who will make a variety of announcements, take the roll call, and then hand the meeting over. Kathleen.

## Administrative Announcements

Ms. Hayes: Thank you, Dr. Monto. Good morning, everybody. My name is Kathleen Hayes, and I'll be serving as the designated federal officer for today's 185th Vaccines and Related Biological Products Advisory Committee meeting.

On behalf of the FDA, the Center for Biologics Evaluation and Research, and the committee, I am 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 the 2024-2025 formula for COVID-19 vaccines. Today's meeting and the topic were announced in the federal register notice that was published on March 4th, 2024, and the amendment published on May 22nd, 2024, made to reflect the change in the meeting date from May 16th to today, June 5th, 2024.

If we could move to the next slide. At this time, I would like to acknowledge the outstanding leadership of Dr. Peter Marks, director of CBER, along with Drs. David Caslow, Jerry Weir, and Sudhakar Agnihothiam with the Office of Vaccines.

Next slide, please. I would also like to introduce and acknowledge my division director, Dr. Atreya, who will be my backup CFO, along with the DSAC team, whose contributions have been critical for preparing for today's meeting. This includes Dr. Suzanne Paydar, Ms. Joanne Lipkind, and Ms. Lisa Johnson.

Next slide. I would also like to express our sincere appreciation to the AB team, Derek Bonner, and Dion Wren, in facilitating today's meeting. Also, our sincere gratitude goes to the many CBER and FDA staff working hard behind the scenes to ensure that today's virtual meeting will be a successful one.

For any press or media-related questions for today's meeting to FDA's Office of the Media Affairs, they can be emailed at fdaoma@fda.hhs.gov. And the transcriptionists for today's meeting include Catherine Diaz and Giselle Liam from Translation Excellence. Next slide. We will begin taking a formal roll call of the committee members and temporary voting members. So when it's your turn, just as a reminder, please turn on your video camera, unmute your phone, and then state your first and last name, organization, and areas of expertise. And then when you're finished, you can turn off your camera and we'll proceed to the next person. So we'll be starting off with our chair, Dr. Monto.

**Roll Call & Introduction of Committee**

Public Health in the Department of Epidemiology, where I've been working for a number of years on vaccines in general, and in particular, epidemiology and control of respiratory infections. Thank you.

Ms. Hayes: Thank you, Dr. Monto. Dr. Berger?

Dr. Berger: Good morning. My name is Adam Berger. I'm a geneticist by training with additional training in immunology. I'm the Director of Clinical and Healthcare Research Policy at the National Institutes of Health. Thank you.

Ms. Hayes: Thank you. Dr. Bernstein?

Dr. Bernstein: Good morning.

I'm Hank Bernstein. I'm a professor of pediatrics at Zucker School of Medicine at Hofstra Northwell in New York, and I have expertise in pediatrics and vaccines. Thank you.

Ms. Hayes: Thank you, Dr. Bernstein. 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 Senior Vice President for Medical Affairs at Rosalind Franklin University in North Chicago. I am a Pediatric Infectious Diseases Specialist with a focus on vaccines. Thank you.

Ms. Hayes: Thank you, Dr. Chatterjee. Dr. Gans?

Dr. Gans: Good morning. Dr. Haley Gans, Pediatric Infectious Diseases at Stanford University. I am the Director of our Pediatric Infectious Disease Program for Immunocompromised Hosts, and my research is on the host responses to antigenic stimuli, including vaccines and also vaccine safety. Thank you. Thank you.

Ms. Hayes: Dr. Janssen, our Alternate Industry Rep for today.

Dr. Janssen: Hi, I'm Rob Janssen. I'm Chief Medical Officer at Dynabax Technologies. I have a background in virology, epidemiology, and clinical development.

Ms. Hayes: Thank you. Captain Sarah Meyer?

Cap. Meyer: Good morning.

I'm Officer of Pediatrics and Vaccines.

Ms. Hayes: Thank you. Dr. Offit?

Dr. Offit: Yes. Good morning.

My name is Paul Offit. I'm an attending physician in the Division of Infectious Diseases at Children's Hospital of Philadelphia and a professor of pediatrics at the University of Pennsylvania School of Medicine.

My areas of interest are mucosal vaccines and vaccine safety. Thank you.

Ms. Hayes: Thank you. Dr. Perlman?

Dr. Perlman: Good morning. I am Stanley Perlman. I'm a Pediatric Infectious Diseases expert at the University of Iowa, and I've been working with coronaviruses for over 40 years now.

Ms. Hayes: Thank you, Dr. Perlman. Next, we'll continue with a roll call of our temporary voting members, starting with Dr. Gellin.

Dr. Gellin: Thanks. Good morning. I'm Bruce Gellin. I'm currently the Chief of Global Public Health Strategy at the Rockefeller Foundation.

I have background in internal medicine, infectious diseases, epidemiology, and for 15 years ran the National Vaccine Program Office. Thanks.

Ms. Hayes: Thank you. Dr. Hawkins, today's acting consumer representative.

Dr. Hawkins: Good morning. Randy Hawkins, infectious diseases, I'm sorry, internal medicine, primary and critical care, Charles University of Medicine and Science.

Ms. Hayes: Thank you. Dr. Lee?

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

Ms. Hayes: Thank you, Dr. Lee. Dr. Levy?

Dr. Levy: Good morning, everyone. My name is Ofer Levy. I am based at Boston Children's Hospital, and I'm a professor of pediatrics at Harvard Medical School, where I direct the

Precision Vaccines Program, a multidisciplinary academic program focused on discovery and development of vaccines for vulnerable populations. Thank you.

Ms. Hayes: Thank you. Dr. Meissner?

Dr. Meisner: Good morning to everyone. My name is Cody Meissner. I'm a vaccine subject matter expert at BARDA within the Department of Health and Human Services and supported by Tenel Government Services.

I'm also a professor of pediatrics and medicine at the Geisel School of Medicine at Dartmouth and a member of the Dartmouth International Vaccine Initiative. I appreciate the opportunity to participate in today's discussion. Thank you.

Ms. Hayes: Thank you, Dr. Meissner. Dr. Nelson?

Dr. Nelson: Good morning, Michael Nelson, professor of medicine and chief of the asthmiology and immunology division at the University of Virginia, trained allergist, and immunologist. I have an interest in vaccine immune response and rare adverse events.

It's great to see everybody again.

Ms. Hayes: Thank you, Dr. Nelson. Dr. Sawyer?

Dr. Sawyer: Good morning.

I'm Dr. Mark Sawyer. I'm a professor of pediatric infectious diseases at UC San Diego, and my area of expertise is in the implementation of vaccine recommendations.

Ms. Hayes: Thank you. And Dr. Wharton?

Dr. Wharton: Good morning. I'm Melinda Wharton. I've been in CDC's immunization program for many years, and my current work is focused on vaccine policy, my training is in adult infectious diseases. Thank you.

Ms. Hayes: Thank you. Thank you, everyone, for the introductions.

**Conflict of Interest**

So we do have varied expertise on the committee, and for today's meeting, we have a total of 17 participants, which includes 16 voting and one non-voting member. So at this time, I will now proceed with reading the conflict-of-interest disclosure statement for the public record. The Food and Drug Administration is convening virtually today, June 5th, 2024, for the 185th meeting of the Vaccines and Related Biological Products Advisory Committee, VRBPAC, under the authority of the Federal Advisory Committee Act of 1972.

Dr. Arnold Monto is serving as the acting chair for today's meeting. Today, on June 5th, 2024, the committee will meet in open session to discuss and make recommendations on the selection of the 2024-2025 formula for COVID-19 vaccines. This topic is determined to be a particular matter involving specific parties.

With the exception of the industry representative member, all standing and temporary voting members of the VRBPAC are appointed special government employees, FGEs, 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 of this committee's compliance with federal ethics and conflict of interest laws, including but not limited to 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public. Related to the discussions of this meeting, all members, RGE and SGE consultants of this committee have been screened for potential financial conflict of interest of their own, as well as those imputed to them, including those of their spouse or minor children, and for the purposes of 18 U.S.C. 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. The FDA has determined that all members of this advisory committee, both regular and temporary voting members, are in compliance with federal ethics and conflict of interest laws.

Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular government employees who have financial conflict of interest when it's determined that the agency's need for a special government employee services outweighs the potential for 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 service which the government may expect from the employee. Based on today's agenda and all financial interests reported by committee members and consultants, no conflict-of-interest waivers have been issued under 18 U.S.C. 208 in connection with this meeting. We have the following consultants serving as temporary voting members.

Doctors Bruce Gellin, Randy Hawkins, Jeanette Lee, Ofer Levy, Cody Meisner, Michael Nelson, Mark Sawyer, and Melinda Wharton. Dr. Robert Janssen of Dynamax Technologies will serve as the alternate 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 special government employees and are screened and cleared prior to participation in the meeting.

They are voting members of the committee. Disclosure of conflicts of interest for speakers follow applicable federal laws, regulation, and FDA guidance. 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 have been screened for their conflict of interest and are cleared to participate in today's meeting. These include Dr. Ruth Link-Gelles, Commander, U.S. Public Health Service, Vaccine Effectiveness Program Lead, the Coronavirus and Other Respiratory Viruses Division within the National Center for Immunization and Respiratory Diseases at the Center for Disease Control and Prevention. Dr. Natalie Thornburg, Acting Chief in the Laboratory Branch in the Coronavirus and Other Respiratory Viruses Division within the National Center for Immunizations and Respiratory Diseases at the Center for Disease Control and Prevention.

Dr. David Wentworth, Chair of the Technical Advisory Group on Coronavirus Vaccines with World Health Organization. Dr. Kayvon Modjarrad, Executive Director in Viral Vaccines and Immunology and Vaccine Research and Development with Pfizer Incorporated. Dr. Darren Edwards, Executive Director COVID-19 Program Lead with Moderna Incorporated.

Dr. Francis Priddy, Executive Director for Clinical Development and COVID-19 Vaccines with Moderna Incorporated. And Dr. Robert Walker, Senior Vice President and Chief Medical Officer with Novavax. Disclosure of conflict of interest for speakers and guest speakers follow applicable federal laws, regulations, and FDA guidance.

FDA encourages all meeting participants, including open public hearing speakers, to advise the committee of any financial relationships that they 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 products or firm not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participant needs to inform

the DFO and exclude themselves from the discussion, and their exclusion will be noted for the record. This concludes my reading of the conflict-of-interest statement for the public record, and I would like to hand the meeting back over to our Chair, Dr. Monto.

**Introduction: Jerry Weir, Ph.D.**

Dr. Monto: Thank you. Thank you, Dr. Hayes. Next, it's my pleasure to call upon Jerry Weir, Director, Division of Viral Products of CBER, FDA, who will give us the introduction and tell us exactly how we're going to have a vote and discussions this afternoon, Dr. Weir.

Dr. Weir: Thank you, Dr. Monto, and good morning, everyone. As Dr. Monto said, I'm going to provide just a brief introduction to the meeting today.

Okay, so to remind everybody the purpose what we're here for today, it is to review SARS-CoV-2 surveillance and epidemiology data, genetic and antigenic characteristics of recent virus isolates, serological responses to current vaccines, and the availability of candidate COVID-19 vaccines for 2024-2025 formula. And then the committee will make recommendations for the composition of the 2024-2025 COVID-19 vaccine formula for use in the United States.

This is an outline of the agenda today. After this introduction, we will hear an update on current epidemiology of the COVID-19 pandemic and SARS-CoV-2 variants from Dr. Natalie Thornburg, CDC, then an update on COVID-19 vaccine effectiveness from Dr. Ruth Link-Gelles of CDC, followed by a presentation from the WHO TAG-COVAC group with their April 2024 recommendation on the antigen composition of COVID-19 vaccines.

This will be given by Dr. David Wentworth at CDC, but he will be giving this as his role as the chair of this WHO technical advisory group. We'll then hear from each of the manufacturers of U.S. licensed and/or authorized COVID-19 vaccines. They'll give brief presentations of their recent work, where they are in the process.

This will be Moderna followed by Pfizer-BioNTech and Novavax. And then I'll come back and give some FDA considerations and recommendations for changes to the vaccine formula composition. It'll be somewhat repetitious of what you've already heard, but hopefully we can summarize everything and lead everyone into the question and answers and the voting questions.

Most of the committee members have been here for the last two years, but I thought I would quickly just remind everybody of the process that we use for this strain composition recommendation process. So as previously proposed in January of 2023, 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.

During the past several months, the FDA reviews these various types of data, the ones listed below in the sub-bullets, and we engage with key partners generating this data, including vaccine manufacturers, as well as other government agencies. The type of data include 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 antibody responses generated by the current vaccines against more recently circulating virus variants, and any available post-infection human serology studies in order to evaluate antibody responses generated by recently circulating virus variants. And then also we look at preclinical immunogenicity studies to evaluate immune responses generated by new candidate vaccines.

In other words, those expressing or containing updated variant spike components. And we look at these against antigenically distinct circulating virus variants. The FDA reviews the discussions and recommendations put forth by other regulatory groups and public health

agencies, and we always discuss these manufacturing timelines with each of the manufacturers of the authorized approved COVID-19 vaccines in order so that we can understand the impact of the strain composition recommendation on vaccine availability.

The next slide shows an overall schematic of this process, where we are now is in the top left where we're reviewing the integrated data to determine the need for an updated composition recommendation, and the VRBPAC and the Little Red Star meeting to make a recommendation discussion today. And then after this discussion, the FDA will make a recommendation to the manufacturers, and then each of the manufacturers will update their vaccines according to these recommendations, and they will submit data packages to the FDA for review. Those types of data packages include exhaustive chemistry manufacturing control data, as well as all sorts of non-clinical data, including animal studies, as well as other non-clinical data.

And then each manufacturer will also begin a clinical immunogenicity trial, which will extend for the next several months. This is mainly to generate the data to continue this process of evaluating how the vaccines do. The approval and authorization of these new modified or updated vaccines occurs within the next couple of months.

And then, of course, in the top right, you see what's called real-world evidence of updated vaccine effectiveness. That's where we use the data that comes from these immunogenicity studies to see how the vaccine's doing during the year and prepares to start the process again, as shown in the bottom right.

The last slide I think I have is just one quick comment about our efforts for global alignment of these strain composition recommendations. As everyone that's been through this for a couple years knows, we have quite a few challenges for global coordination of the COVID-19 vaccine strain composition. This is due to a variety of reasons. But nevertheless, global public

health agencies and vaccine regulators meet throughout the year in an effort to align the criteria used in the vaccine strain composition recommendations whenever possible.

To give you one example, there is something that is called the International Coalition of Medicines Regulatory Authorities. This is an informal group of international regulatory authorities. We meet periodically.

There was actually a workshop held in February of this year, February 26th and 27th, titled Global Perspectives on COVID-19 Vaccine Strain Update, Alignment on the Timing and Data Requirements. The goal of this workshop was to align to the extent possible the evidence required for and the timing of recommendations on updated vaccine composition, to understand the time required by manufacturers to develop vaccines with an updated composition, and to understand the regulatory and timing requirements for regulatory approval. The meeting report from this workshop was recently released, and I'll put the link on the slide for anyone that's interested.

In addition, there is of course a WHO technical advisory group on COVID-19 vaccine composition, so-called TAG-COVAC, which you'll hear from today. The TAG-COVAC issued a statement on April 26th of 2024 on the antigen composition of COVID-19 vaccines, and you'll get the update presented at this door packed by Dr. David Wentworth. But the summary statement of this recommendation was, as the virus is expected to continue to evolve from JN.1, the TAG-COVAC advises the use of a monovalent JN.1 lineage as the antigen in future formulations of COVID-19 vaccines.

So that's all that I have for the introduction, but the next two slides I want to show the voting questions and the discussion topics so that everyone can have it in their mind as we go

through the following presentation. Next slide, please. This will be the one voting question that we have for the committee today.

For the 2024-2025 formula of COVID-19 vaccines in the U.S., does the committee recommend a monovalent JN.1 lineage vaccine composition? This will be a yes or no or abstain voting question. And then after this voting question, we'll have the following discussion topic. Next slide, thank you.

The discussion topic for the day will be based on the evidence presented. Please discuss considerations for the selection of a specific JN.1 lineage strain. For example, JN.1, KP2, and there'll be, as you'll see, several other possibilities for the JN.1 lineage for COVID-19 vaccines, 2024-2025 formula to be used in the U.S. So that concludes the introduction. Thank you. And if there are any questions, I'll be happy to try to answer them.

Dr. Monto: Any questions for Dr. Weir? Dr. Gellin?

Dr. Gellin: Jerry, thanks for that. I really appreciate that. It sets it up nicely. You know, the difference between the discussion topic and the voting questions is in the parentheses. And so I guess the question is, we're going to talk all day about this, but the vote is about the JN.1 lineage.

The discussions include subsets of that. And we're not going to be voting on subsets, it sounds like, based on the questions. Could you comment a little bit about that and what a yes vote would imply on the ultimate selection of a strain?

Dr. Weir: Well, okay. So the voting question will be a yes for the JN.1 lineage. I think that as you go through the day, you'll see that that's a fairly straightforward question, and it's also based on the WHO tag COVAC recommendation. The discussion question is a little more diffuse, and that is because, as you'll also see as we go through the day, JN.1 has continued to evolve, and it makes it somewhat difficult to pick the particular specific strain to be used.

And so we're looking for input from the committee about, get your thoughts about this, and you'll probably be weighing the same things we do, trying to make predictions, but at the same time, see how it affects manufacturing timelines. I will say that this is the approach we've used the last couple of years. We've done it kind of the same way, where we pin the committee down for a general specific voting question for update, and then ask them to comment on the possible choices. And I think it's worked pretty well the last couple of years. Over.

Dr. Gellin: Thank you.

Dr. Monto: Dr. Levy.

Dr. Levy: Yes, thank you, Dr. Weir, for that very helpful introduction. I had a question about some terminology at FDA.

You alluded to this a little bit. Can you help guide us about the distinct differences in immunogenicity data when we talk about preclinical immunogenicity data, non-clinical immunogenicity data, and clinical immunogenicity data? Because I know FDA just tries to create these categories, but they're not always that intuitive. And I may have missed something, but this term non-clinical seems to have come in, I don't recall it used as much in a prior briefing document.

So I don't want to take too much of your time, but if it helps clear up some confusion, it might help down the line in today's discussion. Thank you.

Dr. Weir: No, I'm sorry. There is a little confusion, and I'm guilty of it too. Okay, so clinical is obvious. Clinical data is what goes into people in clinical trials and clinical studies.

Most of us have over the years used preclinical to refer to animal studies. You're right that there is a move to replace preclinical with non-clinical, but I at least view non-clinical as being

more than animal studies. So you do see the term somewhat interchangeably, but yes, there is a movement to start using the general category of non-clinical.

But I think you'll also see manufacturers will still use the term preclinical too, and I've used it many times in my presentation. I think when you hear preclinical in this VRBPAC today, people are talking about animal studies.

Dr. Levy: I got it, but then specifically now, can we hone in on potential differences between clinical immunogenicity data and non-clinical immunogenicity data, setting aside the whole preclinical?

Dr. Weir: Okay, but clinical is always human data

Dr. Levy: Yes.

Dr. Weir: Okay, and so preclinical will be non-human data, even if whether it's animal or if it's non-clinical, it could include some other types of data. Got it. An FDA Modernization Act 2.0 allowed for use of human in vitro systems to support some information. Would data from human in vitro systems fall into which category? I think it would, but I don't think you're going to hear any of that today.

Dr. Levy: Okay, thank you.

Dr. Monto: Thank you, Dr. Meissner.

Dr. Meissner: Thank you, Dr. Monto, and thank you, Dr. Weir, for that introduction. A question I would like to ask relates to the complexity. If the composition of the vaccine differs between the recommendation from, for example, the WHO and our recommendation today, what, how complex a problem is that for the pharmaceutical manufacturers, and can they, could they deal with such a situation? It may not be a question to answer right now, but hopefully the manufacturers can address that as we move forward. Thank you.

Dr. Weir: So I will give you the short answer, but you're right, the manufacturers are best suited to answer it specifically. What you will hear, though, later today is most manufacturers have already done some at-risk work to try to be prepared for various choices. Obviously, no one can be prepared for all the possible choices, but you will hear that, and you will hear from each of the manufacturers about how the choice affects their particular timeline, and it is true that different manufacturing technologies may be affected more than other ones, depending on the choice. Dr. Meissner: Yeah, and specifically, I'm interested in whether or not the manufacturers could make different vaccines with different strains at the same time.

Dr. Monto: Isn't that something which we can bring up again during the discussion? That's the whole purpose of the discussion.

Dr. Weir: You're right, and you will hear a lot of information from this from the manufacturers. They're prepared to talk about this.

Dr. Meissner: Thank you.

Dr. Monto: Dr. Marks, you had something?

Dr. Marks: No, Dr. Weir got to it, which is I think the manufacturers, we have seen the issue of having potential JN.1 versus KP2 discussion or KP variants now, other KP sub-variants coming for a while. The manufacturers, I think, are very well prepared to speak to their ability to address this.

I would just encourage, again, the committee today to focus on what makes the most sense from a scientific point of view, because I think that as you'll hear from the manufacturers themselves, they have done the pre-work to ensure that they are most able to follow what is most appropriate from the scientific and medical standpoint. Thanks.

Dr. Monto: Thank you, Dr. Marks. Dr. Bernstein, the last question.

Dr. Bernstein: Thank you, Dr. Weir, for the great overview of today's meeting. I just had a quick question. The word is used as a vaccine campaign, and I was interested to know what the definition of a vaccine campaign is. Are we thinking of COVID-19 as seasonal, similar to influenza, or annual? I wasn't exactly sure when I was thinking about a vaccination campaign.

Dr. Weir: Yeah, I'm not sure we have a formal definition of it, but I think we are thinking in terms of, well, it started out with the discussions we've had for the last two years about how often can we realistically do this, and I think we pretty much settled on that once a year is practical more than that will depend on other circumstances like emergencies, and so we tend to use the phrase campaign sometimes kind of analogous to the influenza campaign.

I don't know that we have a formal definition for it, but we are starting off with asking you what you think about modifying the vaccine for the upcoming fall winter season, because that's when, of course, cases usually rise. I don't know if anyone else wants to comment on the word campaign or not, but –

Dr. Monto: Dr. Weir, I was a little surprised at the use of the word campaign, which to some people has certain connotations and to other people different connotations. So is it necessary to use it, Dr. Marks?

Dr. Marks: I think it was used because as the ACIP will take the recommendations from VRBPAC and move forward, it was anticipated that in the fall when people get their flu vaccines in whatever you want to call it, we won't use that word which might have political connotations to it, in the seasonal effort to maximize protection of the population against respiratory viruses, it was anticipated that they might receive an influenza vaccine as part of that seasonal effort along with a COVID-19 vaccine as part of that seasonal effort, and we'll leave anything with political overtones out of this. We'll call it a seasonal effort. Okay, thanks.

Dr. Monto: We've got enough issues without having to deal with that.

Dr. Marks: Well, we can call it our seasonal effort.

**CDC Presentation: Update on Current Epidemiology of the COVID-19 Pandemic and SARS-CoV-2 Variants**

Dr. Monto: Thank you. Very good. I like that. Okay, thank you all. We're moving on now to presentations from the Center for Disease Control.

We have a modification of the order that many of you will see on your agenda. First, we are going to hear from Dr. Natalie Thornburg, the acting chief of the laboratory branch within the new Center for Coronaviruses, not Center, Division of Coronaviruses and Other Respiratory Viruses, and then we will hear from Dr. Ruth Link-Gelles from the same division, who will be talking to us on the update of the COVID-19 vaccine effectiveness. So, we're going to hear first from Dr. Thornburg about some of the immunology, antibody responses, and then from Dr. Gelles, we will reserve our questions to the end of Dr. Link-Gelles' presentations and have 10 minutes at that point. So, please, Dr. Thornburg, you're next.

Dr. Thornburg: Thank you. Next slide, please. All right. Today, I'm going to be touching on two things. I'm going on the current epidemiology of COVID-19 and then going through the genetics and the lineages that are circulating right now of SARS-CoV-2.

So, this is a summary of our current situation of circulating in the United States. This timeline covers March of 2020 to the end of May 2024, and you can see weekly deaths in the blue bars, and then on the right Y-axis in the orange line is the weekly percent test positivity. That weekly percent test positivity gives us a good indication of community circulation. Right now, we're sitting in a bit of a trough and sitting at between three and four percent test positivity. During the peak circulation, the highest we've ever observed in percent positivity was around 30

percent, so three out of 10 tests, people who went to get tested for SARS-CoV-2 were positive for SARS-CoV-2, and that was during the Omicron surge in late 2021, early 2022.

This is our trends in COVID-19 associated hospitalization rates covering 2020 to current time period. Each line represents a year, a different year, and so they're stacked on top each other.

The current year is red, 2023-2024, and what you can see is sort of there around between May and June, which is where we are right now, is fairly low hospitalization rates, so we're sitting at hospitalization rates as low as we have observed since about March of 2020, so a little more than four years ago.

We have been tracking seroprevalence of antibodies against SARS-CoV-2, both vaccine-induced, infection-induced, and what we call hybrid immunity.

Hybrid immunity means that some persons who have been both vaccinated and infected at some point, and so you can see the increase of seroprevalence throughout the year in 2020, with most of that dramatic increase were from vaccination-only seroprevalence, and that's gray. The infection-only seroprevalence are the blue bars, increased kind of slowly and plateaued between 2022 and 2023, our most recent data being November 2023. And the hybrid immunity bar, the orange bar, has been increasing slowly over time as well. But we're sitting at about just below 100% seroprevalence, so nearly the entire population has experienced either infection, vaccination, or both infection and vaccination as evidenced by antibodies against the spike in the nucleic acid protein in SARS-CoV-2.

All right, so that's our current epidemiology situation, and now I'm going to go into the genetics of SARS-CoV-2. So this is a slide I showed last year, so this is old data, but I just wanted to remind you of what the genetic landscape looked like last year.

So last year, we saw in the beginning from January 2022 to about November 2022, we saw BA.4, BA.5, and their sublineages circulating widely, and those are shown in orange, green, yellow, aqua. And then right around winter 2022 to 2023, we saw a strain replacement from BA.5 to XBB.1.5 lineage virus. The only time we had observed that previously was delta to omicron shift, and that shift was correlated with a really huge spike in infections.

And last year, we saw a surge in infections as we've been seeing sort of every winter season, but it wasn't nearly as dramatic as we observed in that delta to omicron shift. That is despite the fact that there were quite a large number of substitutions in XBB.1.5 spike protein, which is the target for neutralizing antibodies, and also the protein that binds to the cellular receptor. That is despite the fact that there were a fairly large number of substitutions in spike in comparison to BA.5. And these are two crystal structures of two different versions of XBB that you were considering last year, and the substitutions in spike in comparison to the then vaccine strain BA.5.

And this is a table with a summary of substitutions in those XBB viruses that I were just talking about in the receptor binding domain, which is the most potent target for neutralizing antibodies in comparison to a reference sequence, BA.4, BA.5. And I'm using that reference sequence here because that was part of the vaccine makeup in the 2020 to 2023 season. So this is what we were considering the change from BA.4, BA.5 to something updated last summer.

All right. So this is current data of the strain circulation, lineage circulation we have observed in the past year from June 2023, so right around the time I spoke to you last year until current.

So we saw XBB.1.5 and similar viruses circulating throughout the summer and throughout the fall. And all of these EG5, FL.1.5.1, HV1, HK3-like, those all sound very

different because of the different letters, but they are all XBB.1.5 viruses, sublineages of those viruses. So we saw XBB.1.5 lineage viruses circulate through the summer last year and into November.

And then in December, much like December of 2022, we saw a strain replacement. This time the strain replacement was JN.1-like. So again, like when we saw BA.5 to XBB.1.5, that was a shift. It was from a different phylogenetic lineage.

The same thing occurred this winter with that shift in JN.1-like viruses. And then much like last year, we have seen a parental lineage circulating in the early winter, and then we start to see diversification in the spring, which is what we're seeing now. And so you can see some pink, some gray, some KQ.1-like, KP.2-like, that is some diversification that we are currently observing, much like we did last late spring, early summer.

So this is the most recent summary of lineage proportions, the weighted estimate, and the now-cast estimate. So this summary was posted on May 24th for the week ending, by week ending May 25th.

We are currently analyzing data for our next reporting period, which we'll post this weekend. So there will be an updated version this coming weekend. And this looks a lot more diverse than it actually is.

So weighted estimates, it's just a reminder, are proportions of the viruses, virus lineages circulating from actual sequences. And then now-cast is a model based on those sequences. So we, using the weighted estimates, we calculate, we estimate growth rates and then predict into the present tense what we think proportions of circulating viruses are.

Now, there is some uncertainty in the now-cast, which is why it's sort of grayed out, because it is a model into the present. And there's a particular amount of uncertainty right now,

because we have a lower number of sequences in the weighted estimates than we have historically. And that's due to combination factors, testing practices, availability of specimens, because there's not a lot of community transmission.

There just aren't a lot of specimens to then sequence. And just, you know, limited laboratory capacities throughout the entire country to maintain the level of sequencing that was maintained two or three years ago. But we still feel fairly, you know, we still feel fairly confident in lineages that are increasing and decreasing.

They just might sort of ride one edge of those confidence intervals. So KP2 and similar viruses are currently the most prevalent viruses in the United States. So there are several groups of viruses that actually have the same spike sequence.

So I'm calling them KP2-like viruses. And that includes KP.2, JN.1.16.1, and a few more. So those are the most prevalent circulating viruses, KP2 and KP2-like viruses. And the second most prevalent viruses that we're predicting are KP3 lineage viruses. Both of those sets of lineages are descendants from JN.1 and are very similar to JN.1. And I will show you that in a moment. But KP2 and KP3 lineages have evolved independently of each other, but both from JN.1.

All right. And so this, I just want to put this into context of sort of how many infections these current lineages might be causing. Because the now cast you are seeing are proportions of viruses. And so it's always scaled to 100% because it's a proportion. It's a percentage. And so this is covering the entire pandemic of SARS, or I'm sorry, not the entire pandemic, the past year of SARS variant proportion scaled by normalized counts of positive tests from our nerves surveillance system from April 2022 to April 2024. And that purple color on the right are JN.1-like viruses.

In the current viruses that we're seeing, KP2-like viruses are pink in that very small little blip that's coming up on the far right. And if you go to the next slide, please, I'll show you a zoomed in version of that. So you can see that sort of epidemic wave that we observed in the winter.

It wasn't all driven by JN.1 viruses. The beginning of that included XBB.1.5 viruses and its descendants. So all those multiple colors on the left side, those are XBB.1.5 viruses.

And then you see JN.1 strain replacement and about half of it, half of the infections this winter were JN.1 and sort of the other half of them were XBB.1.5 lineage viruses. And the current number of infections we're observing right now by KP2, KP3, KP2-like viruses are quite low. Next slide, please.

This is also from our COVID data tracker. This is not a phylogenetic tree. This is just a dendrogram to show you the relationship of recent SARS-CoV-2 lineages. Because of the way that Pango, the software that we use to call lineages, names viruses, when it gives aliases or nicknames, when you get too many numbers, sometimes viruses sound like they're very different and they're not very different. So you can see that strain replacement, if you look on the far left, kind of at the top, B.1.1.529, that was Omicron, B.1.617.2, that was Delta. You can see that sort of shift that happened in 2021, 2022.

Then Omicron evolved to B.A.2. And then it followed a B.A.5 lineage, B.A.4 and B.A.5 lineage. And then we saw the strain replacement the following year to XBB, which was a descendant of B.A.2, but it was a strain replacement because it wasn't in the same lineage as B.A.5. We've observed something similar this year. You saw XBB.1.5 evolve throughout the year.

And then again, it was sort of a B.A.2 lineage that resulted in the JN.1 lineage. And that's sort of up in the top right portion of this dendogram. And now we're seeing JN.1 lineage viruses diversify.

So this is a summary of substitutions that are in the receptor binding domain. So the most important part of this spike protein in comparison to XBB.1.5, the current vaccine formulation. I want you to look mostly on the bottom half of this table where you see the most sort of substitutions pop up is the JN.1, that strain substitution. There were quite a lot of substitutions in the receptor binding domain and throughout the rest of spike protein in comparison to the vaccine strain. But then if you look at the bottom two rows, Kp2-like viruses, those are the lineages that all have the same spike protein, but different names. And Kp3, the bolded lineages means that right now we are predicting that they are increasing in proportion. And what I want you to notice is they are very, very similar to JN.1. There's not a lot of differences. We're really talking about two differences in the receptor binding domain. And when you look at Kp2 and Kp3, they are nearly identical to each other with really one difference between the two of them. So it's two differences for each of those in comparison to JN.1 and one difference between Kp2 and Kp3. Next slide, please.

I'm going to show you a couple of crystal structures. I'm going to show you a couple of crystal structures to just show you the differences we're talking about. So I showed you sort of the dendogram of BA2. This is the number of substitutions in JN.1 in comparison to BA2 and the spike protein.

Take home message, it's a lot. There's a side view, the top view in the middle, and sort of a zoomed in view on the right side of the receptor binding domain, which is the most important part that bind the most potently neutralizing antibodies is to that sort of green and red portion of

the spike protein. And this is a comparison of substitutions that are in JN.1 in comparison to XBB.1.5. It was quite a lot. It caused a lot of concern whenever JN.1 emerged. But Dr. Gellis, Link Gellis will tell you about vaccine effectiveness and how it held pretty well throughout the winter.

And then this is me just showing you again the same slide about substitutions throughout the receptor binding domain. So I just showed you all of these JN.1 substitutions onto the surface of XBB.1.5.

Okay. So here is what we're talking about if we're considering JN.1, KP2, KP3. It's quite a different picture than what I just showed you. So this is the full spike protein. This is substitutions in KP2 in comparison to JN.1 spike protein, KP2, that's on the left. KP3 in comparison to JN.1, and that is on the right. And what you see is there's not a lot of differences. KP2 and KP3 really each have two substitutions in the receptor binding domain, green up there in the top, in comparison to JN.1. They have one substitution in common, and then they each have one different substitution.

Okay. So that is the sequence we're talking about. I believe Dr. Wentworth is probably going to give a little bit more data about antigenicity and antigenic cartography, but this is just a little bit of data, antigenic cartography from mice that Dr. Yulong Cao's group has in a preprint on BioRxiv currently to look at how similar these viruses are to each other.

So the easiest way to do this now, because of our very complex immune history, is using animal models. And in this, they take an animal, expose them to an antigen, collect their sera, and then use that sera for neutralization against a panel of viruses. And then if they cluster together, this is just a way to show neutralization data, to show if viruses are very similar to each other, they cluster close to each other.

So the take-home message I want you to see in this one is that the JN.1 viruses, they're kind of all clustered together on the right side, kind of a quarter of the way or a third of the way up the Y axis. And JN.1, KP2-like viruses, they're really, really on top of each other, and KP3 is very close by, not absolutely on top of it, but very, very close by. And they cluster away from XBB.1.5 viruses, and that is sort of like down and to the left a little bit.

Those are the XBB.1.5 cluster of viruses. So JN.1 descendant viruses, including KP2 and KP3, are antigenically similar using this particular mouse model.

All right, so that concludes my genomics section, and I'm just going to touch very, very briefly on a severity analysis that my epidemiology and our IV network partners did comparing severity of XBB.1.5 lineage infections and JN.1 lineage infections this past season. Next slide, please. All right, so in this study, they examined the clinical severity of COVID-19-associated hospitalizations among adults with sequence-confirmed JN.1 virus versus XBB lineage infections.

In the population of this network, it's the IV network, it's 26 hospitals, 20 U.S. states, and enrolled adults aged 18 years and older who are hospitalized with COVID-like illness, and the SARS-CoV-2 test results within 10 days of illness onset and three days of admission are positive. It's restricted to patients who tested positive for SARS-CoV-2 and had sequence-confirmed JN.1 infections or XBB lineage infections. The period of analysis was from October to March of this past season, winter season, and the first day that the patient was admitted with sequence-confirmed JN.1-like infection, and they looked at the last week during which a patient was admitted with a sequence-confirmed XBB.1.5 lineage infection.

Our partners did multivariant logistic regression and used to estimate the odds of four adverse in-hospital outcomes among patients with JN.1 versus XBB lineage infection, adjusting for confounders. Next slide, please. All right.

And the take-home message I want you to see from this one is that looking at these four different outcomes, use of supplemental oxygen, advanced respiratory support, intensive care admission, or invasive mechanical ventilation or death, is that the adjusted odds ratio of JN.1 infections versus XBB.1, XBB lineage virus infections, was very close to one for all of the outcomes, very close to one with confidence intervals crossing one. And so, therefore, we conclude that JN.1 infections were no more severe than XBB.1.5 or XBB lineage virus infections. Okay.

So the current circulation of SARS-CoV-2 is relatively low. JN lineages have replaced XBB.1.5 lineages during the winter of 2023 and 2024. The severity of JN.1 infections did not appear to be worse than earlier XBB.1.5 infections. JN.1 lineages are currently undergoing phylogenetic diversification. We're seeing convergent evolution of the spike occurring, so we're seeing similar substitutions in the spike, similar substitutions in the spike in different lineages of viruses.

And KP2-like lineages and KP3 lineages are currently predicted to be increasing in proportion. Both of these lineages only have two substitutions in the spike binding domain in comparison to JN.1. And preliminary data indicate JN.1 lineages are antigenically similar. And that's all, and I will hand off the next slide and hand off to Dr. Link-Gelles.

Dr. Monto: Dr. Link-Gelles, please.

**CDC Presentation: Update on COVID-19 Vaccine Effectiveness**

Dr. Link-Gelles: Hi, good morning. If you could go to the next slide. Today I'll be presenting updated COVID-19 vaccine effectiveness data from CDC among children and adults and against

various outcomes. Before we dive into the main content, though, I wanted to share a refresher on VE methods and some context for interpretation of COVID-19 VE.

So there are a number of study designs used for vaccine effectiveness, but the most common COVID-19 VE has been the test negative design or TND. In a TND, everyone who meets a clinical case definition, in this case, persons with acute respiratory illness or COVID like illness, are enrolled, and those who test positive for the disease of interest, in this case, SARS-CoV-2, are classified as cases, while those who test negative are classified as controls.

Finally, vaccination status between cases and controls is compared. In a TND, enrollment is not based on test status, but based on a clinical case definition, and data can be ascertained through electronic health care records or based on clinician-ordered testing or based on active enrollment and swabbing of persons meeting a clinical case definition. VE is then calculated as one minus the adjusted odds ratio times 100 percent, with the adjusted odds ratio comparing the odds of vaccination among cases and controls.

Next slide. So there are a number of benefits to the TND. First, it reduces bias from healthcare seeking behavior by including cases and controls with similar symptoms who presented to care and received testing, usually at the same facility.

Second, TNDs are an efficient use of resources because cases and controls are identified through the same healthcare system or testing location, rather than meeting one system for cases, for example, a hospital, and another for controls, for example, random digit dialing. There are also a couple of considerations for TNDs. First, they're dependent on the sensitivity and specificity of diagnostic testing and can be particularly impacted by decreases in test specificity, which can result in truly negative individuals testing positive and being misclassified as cases.

Second, because vaccination behaviors for different diseases can be correlated, controls who are positive for another vaccine preventable disease can bias results. For COVID-19, it can be helpful to consider if the exclusion of influenza positive controls meaningfully changes estimates. Next slide.

Finally, it's helpful to keep in mind that vaccine effectiveness, like vaccine efficacy, is a population level estimate. If a vaccine has a VE of 80%, it does not mean that the vaccine will only work 80% of the time. It does mean that in a vaccinated population, 80% fewer people will contract the disease when they come in contact with the virus compared to an unvaccinated population.

So now moving on to some context for interpretation of COVID-19 vaccine effectiveness estimates. This graph shows COVID-19 vaccination coverage among children and adults from September 2023 through April 2024, with adults on the left and children on the right. As with previous years, coverage rates increase with increasing age and the lowest coverage rates are in the youngest age groups, which impacts the ability to estimate VE. Next slide. And some additional context for interpretation of VE estimates, it's helpful to see SARS-CoV-2 infection-induced immunity. By July through August 2023, just before the 2324 vaccines were introduced, individuals in the U.S. have high rates of infection-induced immunity, above 70% for all age groups and almost 90% for those aged 16 to 49 years. Infection provides some protection from future infection and VE finding should therefore be interpreted as the incremental or additional benefit provided by COVID-19 vaccination in a population with a high prevalence of infection and vaccination-induced immunity.

So before diving into VE estimates, a note here on what the studies presented today evaluated. Previously for COVID-19, we presented results as absolute or relative vaccine

effectiveness, shown here in the top and middle rows. Absolute VE compares the frequency of health outcomes in vaccinated versus unvaccinated people. For example, those who received a 2324 dose to those who received no COVID-19 vaccine ever. Relative VE compares the frequency of health outcomes in people who received one type of vaccine to people who received a different vaccine. For example, people who received the 2324 dose versus those who received a bivalent dose.

This year, COVID-19 VE studies have largely shifted to looking at a combination of absolute and relative VE. Today I'll present estimates of VE comparing those who received the 23-24 doses to those who did not receive 23-24 doses, regardless of past vaccination history. In other words, the comparison group today includes people who are unvaccinated as well as those who received original monovalent and bivalent doses, and this is similar to how influenza estimates VE most seasons.

Next slide. I'll first share VE against symptomatic SARS-CoV-2 infection from the Increasing Community Access to Testing, or ICAT, program. Data shared today represent updates to analyses that were published in CDC's MMWR at the beginning of February.

Next slide. ICAT includes data from nationwide community-based pharmacy testing for SARS-CoV-2. COVID-19 vaccine history is self-reported at the time of registration, and analyses used a TND.

For this analysis, we included adults aged 18 plus with one or more COVID-like symptoms, and testing via nucleic acid amplification are met. We excluded adults who reported an immunocompromising condition and those who reported a positive SARS-CoV-2 test in the preceding 90 days. The full analysis shared today uses methods previously published in MMWR but is updated with data for May 2024.

A sub-analysis used S gene target failure as a proxy for VA.2.86 and JN.1 infection with slightly different dates. Next slide. Here we have results from the full analysis with people aged 18 and up included in the top block and split by age group 18 to 49 and 50 plus on the bottom.

VE is shown comparing receipt of 2023 to 2024 dose to no receipt of the 2324 dose and by time since receipt of 2324 dose, 7 to 59 days, 60 to 119 days, and 120 to 179 days. In the second column from the right, note that the median time since receipt of last dose, which was almost two years for younger adults and over 1.5 years for older adults. VE for the full period was 45%, and there were less tests in older adults and therefore wider confidence intervals.

As mentioned, we were able to use S gene target failure as a proxy for infection with VA.2.86 and JN.1. This graph shows estimated proportions of SARS-CoV-2 S gene target results in variant proportions in red and blue from genomic surveillance. The red indicates S gene target presence or likely XBB lineages, while the blue shows S gene target failure or likely VA.2.86 and JN.1 lineages. The black line shows the proportion with S gene target presence from ICAT data, which tracks the proportion via genomic surveillance, indicating that S gene target failure is a good proxy here for VA.2.86 and JN.1. The proportion deviates slightly in the most recent weeks when there was relatively little ICAT testing. Next slide. This slide shows results of the subanalysis using S gene target failure.

Because of the timing of emergence of JN.1, there was not statistical power to estimate VE in the days after vaccination. So here we show only the 60 to 119 day period. S gene target presence or likely non-JN.1 lineages is shown in the top with a median of 73 days since the last dose and a VE of 58%. S gene target failure or likely JN.1 lineages is shown in the bottom with a median time since dose of 89 days and a VE of 37%. Note that while the point estimates differ, the confidence intervals between the estimates overlap.

So moving on now to estimates against emergency room and urgent care visits from the VISION network. As with ICAT, these methods were published recently in MMWR, but the results today include additional more recent data. VISION is a multi-state network of electronic health care records using a test negative design. This analysis included adults visiting one of over 300 emergency departments or urgent cares or over 200 hospitals with COVID-like illness and a SARS-CoV-2 NAT test result within 10 days before to 72 hours after the encounter. Cases were patients with a positive NAT for SARS-CoV-2 and no positive NAT for RSV or influenza. Controls had a negative SARS-CoV-2 test and no positive influenza test. Vaccination here is documented by electronic health records and state and city registries. Next slide.

As before, this slide shows results with adults aged 18 and up on the top block and separated into age groups 18 to 64 and 65 plus years on the bottom. And as before, we show VE split by 7 to 59, 60 to 119, and 120 to 179 days since receipt of the 2324 dose. In the 18 plus group where we had the most power, VE was 50 percent in the first 7 to 59 days post-dose, 32 percent in the 60 to 119 days, and 2 percent in the 120 to 179 days after the 2324 dose with non-overlapping confidence intervals.

This same trend was apparent in both age groups and VE was generally similar for 18 to 64-year-olds and for those 65 plus. Next slide. We'll now move on to results from vision and IV networks for VE against hospitalization, which have also been updated since the MMWR in February.

Starting with the vision results and as with previous result slides, we have VE for 18 plus on the top and split by age group on the bottom with results shown by times and dose. VE was 50 percent for 18 plus in the first 7 to 59 days after the dose, 41 percent in the 60 to 119 days after the dose, and 16 percent in the 120 to 179 days with some overlapping confidence intervals.

Note that due to both lower vaccine uptake and lower hospitalization rates, confidence intervals for the 18 to 64 group were wider than for older adults, particularly in a longer time since dose strata. Next slide. Here we have VE against hospitalization split by immunocompromised status.

The estimates on the top are for those without immunocompromising conditions and are the same shown on the previous slide for those 18 plus. On the bottom, VE is for adults with immunocompromising conditions. Trends are similar across the two age groups with point estimates somewhat lower in the immunocompromised group, though confidence intervals overlap.

Here we have VE against critical illness, which is defined as admission to an intensive care unit or death while hospitalized or within 28 days after the hospital admission. As with previous formulations, we see what appears to be more sustained VE for critical illness, the most severe outcome, versus infection and hospitalization, though the confidence interval in the 120 to 179 day group is quite wide.

Moving on now to the IV network, a multi-state VE platform that uses TND with enrollment at 26 hospitals. Participants were adults hospitalized with COVID-like illness. Cases have a SARS-CoV-2 positive NAT or antigen test with no positive influenza or RSV test. Controls are negative for SARS-CoV-2 and influenza by NAT. Vaccination history is ascertained through EMRs, state and local vaccine registries and self-report and specimens are collected for testing and sequencing.

As with the vision results, here we see 18 plus on the top and then split by age group on the bottom. Note that IV analyses did not have statistical power to estimate VE separately by age and time since dose.

In the 18 plus group, VE in the first 7 to 89 days was 41 percent and then in the 90 to 179 days was 27 percent with overlapping confidence intervals. The point estimate for those 65 plus is lower than younger adults with the confidence intervals also overlap.

The IV network also collects specimens and conducts whole genome sequencing. For this analysis, they restricted cases to those with sequence-confirmed JN.1 lineage or XBB lineage infections during October 18, 2023, through March 9, 2024. During this period, sequencing was successful for 63 percent of case patients. This graph shows results of sequencing with XBB lineage admissions in blue and JN lineages in orange. You can see the gradual increase in JN lineages over time taking off in December and January, which matches the national sequencing data.

Next slide. And here we see VE results by lineage with XBB on the top and JN on the bottom. VE estimates are similar to those from ICAT with point estimates showing lower VE for JN lineages but confidence intervals between the lineages overlapping and some protection remaining for JN lineages.

Finally, I'll share some results of VE across age groups including among young children from the VISION network. Next slide. First, as a reminder, young children are recommended to receive more doses than adults. Previously unvaccinated children are recommended for a complete initial series of 2324 vaccine, including two doses of Moderna or three doses of Pfizer vaccine. Children who previously received doses of COVID-19 vaccine are recommended to receive different numbers of doses based on how many previous doses they received, but all young children are recommended to receive a complete initial series, either including or with the addition of a 2324 dose.

This slide shows VE results against emergency department and urgent care encounters in VISION, split by age group and time since dose. The top section includes the referent group, which includes persons who did not receive a 2324 dose, including both unvaccinated persons and those who previously received original monovalent or bivalent doses.

In the middle, we have VE by age group during the 7 to 59 days after receipt of a 2324 dose. You'll notice that the youngest age group is those nine months to four years of age. The nine-month cutoff was used to allow time for six-month-olds who are newly eligible for COVID-19 vaccination to complete the Pfizer primary series, which takes 13 weeks. You'll see that VE is similar across age groups with wider confidence intervals in children due to both lower vaccine coverage and lower SARS-CoV-2 positivity. The bottom section includes VE in the 60 to 119 days since the 2324 dose, and here the confidence intervals for the youngest children are really too wide to interpret, but the other age groups look similar.

Finally, just some conclusions of vaccine effectiveness for the COVID-19 vaccine during the 2324 season. These vaccines provided increased protection against symptomatic SARS-CoV-2 infection and COVID-19 associated emergency department and urgent care visits and hospitalizations compared to no receipt of the 2324 vaccine dose. Waning patterns appeared similar to previous COVID-19 vaccine formulations, and with the most durable protection appearing to be for critical illness, though statistical power was lacking in the longest time period since vaccination.

As with previous COVID-19 formulations, effectiveness was similar across age groups, and receipt of the 2324 COVID-19 vaccine provided protection against JAN.1 and other circulating variants, though that protection may be lower than that provided against SBV

sublimated variants. I'd like to thank the many investigators who contributed to these analyses, including vision and IV site investigators and CDC staff. Thank you.

Dr. Monto: Thank you both for your very clear presentations of a lot of data. We now can have our initial discussion. Please keep in mind that we are yet to hear from Dr. Wentworth, who will be presenting the views of the technical advisory group of WHO. So, Dr. Levy.

Dr. Levy: Yes, I'd like to thank both speakers in this session for their excellent presentations. I had a big picture question. Given the different types of data that are being collected and considered, clinical data and surveillance data on the virus, sequencing data about the protein structure, the amino acids in the spike protein for the prevalent variants, vaccine efficacy, etc., all these different types of data, is there any federal effort to try to integrate these data and use approaches such as machine learning, artificial intelligence, to see if we can predict from a particular mutation what the implications will be for cross-reactivity of sera and or for clinical disease and vaccine efficacy? Obviously, at the end of the day, what we most care about are the safety and efficacy of the vaccines. But to the extent that we can model this in silico, obviously, we can get even faster and even smarter. So, I'm just wondering if there's any such federal effort. Thank you.

Dr. Monto: I assume this is a question for CDC, so either of you can jump in.

Dr. Thornburg: Yeah. We don't have an exact project like that going on right now in our program. Our Center for Forecasting Analytics are always developing new modeling and new predictor tools. And so, they have many, many projects in the works. And we're always trying to improve our now-cast modeling and would love in the future to be able to incorporate some more complex data than just genetics.

Dr. Monto: Thank you. Dr. Offit?

Dr. Offit: Yes. Thank you for those presentations, which are very clear. My question actually is for Dr. Thornburg. Dr. Thornburg, do you have more granular data on who is getting hospitalized and who is dying? Meaning, what are their ages? What are their comorbidities? When was their last dose of vaccine? If they were in a high-risk group, did they take an antiviral? I'm just trying to figure out who we're missing, who's getting hospitalized, and who's dying.

Dr. Thornburg: Yeah. So, that data that I showed, they do have all of that information in that hospitalization data in our IV network that collects that information. And I don't have it. Everything in that particular analysis was adjusted. So, age-adjusted, vaccine-adjusted.

So, it was all adjusted just to compare the severity of the infection outcomes by different lineages. We do have that information, and I don't have it at my fingertips.

Dr. Offit: Will you be publishing it?

Dr. Thornburg: Type it in the chat.

Dr. Offit: Natalie, will you be—Yes. Our IV network colleagues will be publishing that.Thank you.

Dr. Monto: And it is stratified by duration since last vaccination, correct?

Dr. Thornburg: Well, that analysis that I showed today was independent of vaccination. So, the vaccination analysis that is –

Dr. Monto: Well, I'm thinking the VE presentations were mainly stratified since last vaccination, were they not?

Dr. Thornburg: Yeah. So, I can provide a little bit of additional information.

Dr. Monto: Please.

Dr. Thornburg: Data from both the VISION and IV networks, descriptive information about underlying conditions, age distributions, and things like that were published in the CDC MMWR

in February, and both networks plan to publish much more lengthy presentations of that information over the summer.

I will say that I think we've continued to see similar trends as past years where those with the most severe illness and those most likely to die are those that are unvaccinated, and that's evidenced by the vaccine effectiveness estimates that I showed on critical care from the VISION network. I will say that we do continue to see both children and adults without underlying conditions needing hospitalization and or dying. So, for example, in the COVIDNet platform, which is our main surveillance platform for COVID hospitalizations, 50 percent of the kids that died had no underlying conditions, and this, I think, emphasizes the need for vaccination regardless of underlying condition status or age.

Dr. Monto: But waning continues to be an issue and complicates trying to separate out lineage received from vaccine efficacy.

Dr. Link-Gelles: That's true. We do continue to see waning of vaccine effectiveness, and because that's inextricably linked with time, as with new variants, it's difficult to parse out how much loss of effectiveness over time is due to waning versus new variants.

I will say that we continue to see the same patterns as past years, including the most sustained effectiveness against the most severe illness or critical illness, which we've defined as admission to intensive care unit and death.

Dr. Monto: Thank you. Dr. Gellin.

Dr. Gellin: Thanks. Actually, on that last one, are you also able to stratify by product? I also want to thank both of you for the great presentations. But for Dr. Thornburg, I think it was probably in the fine print, but the source of the materials that are then sequenced are from clinical samples.

You don't get them from people who test at home. I'm curious about whether or not wastewater has a similar sort of, if you're able to do the same in wastewater, and if it's got a similar profile. Thanks.

Dr. Thornburg: Yeah. I mean, our wastewater testing program does do, like, follows the signal over time. I didn't show any of that data, and they can also estimate variant proportions. It's a little bit more complicated to parse out proportions in wastewater because there are so many confounding factors. It is by nature a mixed specimen, whereas for sequencing from clinical specimens, we know that this one specimen is from one person. And if we test 10,000 specimens, then it's more simple math than these wastewater, which we don't know how many infected people this is coming from.

But when we have looked at wastewater proportions and compared it to our clinical proportions, aggregate, they're similar, but we do see some data anomalies. Like, if we look at individual communities, sometimes we can see a lineage that's way out of scale for proportion when we compare to our clinical testing, maybe due to some small outbreak or, like, a super shutter or something like that. So having both sets of data, it's a good sanity check that, yes, we're seeing it in wastewater and we're seeing it in clinical sequencing, and that helps us feel more confident in our results.

Dr. Monto: Thank you. Dr. Gans.

Dr. Gans: Thank you both. I really appreciate that. My questions are sort of similar to those that have been going on, the more granular data. I think we need to really understand how to target our populations, but also in terms of predictions.

So what we're seeing is this pattern of strain replacement that happens when there's more circulation of the virus. So it's seeming like it is taking some temporal patterns of that happening

in the winter and then the lineage diversification. So similar to what we do with flu and other things, I think we need more of a global look at what is happening to areas where that happens before it happens in the U.S. to really predict. I mean, we're making global sort of recommendations as well, but I feel like that data still needs to be part of the conversation so we can predict a little ahead and see what the next strain replacement might be so that we could be better prepared for that. Is there any efforts to overlay that data for us so that we can sort of see that happening?

Dr. Monto: Anybody? We are going to hear from Dr. Wentworth with the WHO view, so maybe we can park that until we hear what WHO is doing and then come back at a later time. Dr. Meissner?

Dr. Meissner: I'd like to add my thanks to Dr. Link-Gelles and Dr. Thornburg for those presentations. I think that the questions that Dr. Offit asked is so important when we begin to think about the relative benefit versus harm for different age groups. So I think further clarification of that data will be very helpful. But the question I have for Dr. Thornburg, could you just briefly tell us about the weighted and now-cast estimates? How many isolates are typically included? I think you said the number is going down because there is less disease around, obviously.

But how representative are they of the United States geographically and age-wise? Over.

Dr. Thornburg: Well, okay, so geographically, as far as geographic distribution goes, the weighting is by state and it's by population of the state. And so if we have a lot of sequences from one state, then we use that weighting to make sure that those sequences aren't skewing our national picture. So that's one of the reasons why we do weighting. And we do have coverage

across the United States. Of course, we do have a lot more specimens available in some parts of the country and a lot more sequencing available in other parts of the country.

So there are a few regions in the country which are generating a lot more sequences than others. And we try to adjust as best we can. As far as age, we don't collect a lot of metadata with our sequencing.

We ask that our specimen submitters and that our sequencing labs for the sequencing we don't do locally, that they do a random sampling. So we don't get a lot of metadata, really much metadata except for date of collection, location. We just specifically ask that specimens are not linked to an outbreak per se and that they get temporal distribution and whatever is representative that's happening in their community.

Dr. Meissner: Can you tell us how many?

Dr. Monto: We're going to have to move on right now because we have a number of people with hands raised and we want to keep to schedule. We have a lot of time this afternoon for further discussion. Dr. Perlman.

Dr. Perlman: So I just had a question about some of the vaccine efficacy measurements. So I think there are data that most of the antibody response, no matter where it started, is against the ancestral strain and that there's actually very little variant specific antibody responses. And then in addition, there's other data showing that time after a vaccination, even with the ancestral vaccine, that there's broadening of the immune response that covers these new variants.

So with that kind of information, how do you think about that? Or has the CDC independently done any of those assessments? Because it might imply that the actual target may not matter so much as long as people are vaccinated once a year because you're basically

boosting the same antibody because So the people talk about antigenic priming, but in fact it may be useful here.

Dr. Link-Gelles: So I'll let Dr. Thornburg comment on the immunogenicity piece of it, but I will say on the clinical effectiveness side, because the United States has never had two different formulations of the vaccine approved for the same people at the same time, we've not been able to separate out the potential effect of, for example, receiving a bivalent or original monovalent vaccine as recently as receiving a 23-24 dose. So at least on the clinical vaccine effectiveness side, all we can look at is time since dose, and we can only look at the specific formulation that's currently approved.

Dr. Monto: Thank you, Dr. Nelson.

Dr. Nelson: Thank you, Dr. Monto. Mike Nelson, congratulations again, a very thorough presentation with a lot of data that was very clearly presented and easily digestible. My question is for Commander Link-Gillis. You presented data on vaccine efficacy in the immunodeficiency population from the Vision Network. In this context of waning durability and waning efficacy over time and the ability for individuals to receive multiple vaccines throughout the year as a recommendation for the immunodeficient population, my question is, do we have any data on those individuals who received multiple doses throughout the year, and is the vaccine efficacy data presented from the Vision Network influenced by multiple vaccines received by that population? Thank you.

Dr. Link-Gelles: Right, so immunocompromised individuals are currently permitted to receive a vaccine every two months with a conversation with a provider. So in theory, you could have a non-immunocompromised person with a single dose of the 23-24 vaccine this year, but an immunocompromised person with a handful of doses at this point. I will say in our data in the

Vision Network, the number of people that are immunocompromised that actually go out and get multiple repeat doses is very small, and that's not just been true this year.

That was true last year and the year before as well. So we've never had statistical power to look at someone who truly received a dose every two months. In a paper, I believe it was last fall, looking at the two falls ago, looking at the bivalent dose in immunocompromised individuals, we were able to look at those who received at least one extra dose and saw similar patterns. So not surprisingly, I think, you know, the immunocompromised individuals tend to track overall similar patterns of vaccine effectiveness of non-immunocompromised people, often with VE just a little bit lower than in the otherwise healthy population. Understood. Thank you.

Dr. Monto: Thank you. Last question before we move on, Dr. Chatterjee.

Dr. Chatterjee: Thank you, Dr. Monto. My question is also for Commander Blake-Ellis. You presented data on symptomatic disease, I believe, ED visits and hospitalizations. I don't recall seeing data on the use of assisted respiratory technologies, you know, ventilation and deaths related to vaccine effectiveness. Can you comment on that? I thought I heard you say that the deaths were mostly in people who are unvaccinated. But can you shed a little bit more light on the more severely ill patients and the deaths?

Dr. Link-Gelles: Sure. So slide 20 in my presentation was VE against critical illness. That's from the Vision Network, which defines critical illness as admission to intensive care unit or death. Because it's EHR-based, receipt of supplemental oxygen is not well-collected in that platform. The IV network has been able to look at receipt of invasive mechanical ventilation as part of a critical illness and point in them as they were not powered this season just due to overall lower uptake of the vaccine and lower rates of disease. But I can say in past seasons, and the Vision Network data tracks what we saw last season, we do generally see much more sustained vaccine

effectiveness, even of the original monovalent vaccine as well as the bivalent vaccine against the most critical illness. So while we see quite a bit of waning, so almost negligible protection against hospitalization, we've seen critical illness vaccine effectiveness maintained out to a year or two years after a dose. So we know that the vaccines are continuing to provide some protection against the most severe illness long after receipt. Thank you.

**WHO Presentation: WHO TAG-CO-VAC May 2024 recommendation on the antigen composition of COVID-19 vaccines**

Dr. Monto: Thank you. We're moving on now. Next we're going to hear from Dr. David Wentworth, who is representing the Technical Advisory Group at WHO in terms of their recommendation. Dr. Wentworth is familiar to our committee from previous involvement with influenza. He is now at CDC, the Director of the Coronavirus and Other Respiratory Viruses Division. Dr. Wentworth.

Dr. Wentworth: Thanks very much, Dr. Monto. Can you hear me okay and see the slides? Dr. Monto: Yes.

Dr. Wentworth: Okay. So I'm going to get going here. So the TAG-COVAC, as Dr. Weir already introduced, is a WHO committee. And our job in the context of today's discussion is to recommend to WHO for each COVID-19 vaccine platform adaptations, if any, needed so that vaccines continue to safely provide protection against SARS-CoV-2 variants. And currently, the TAG-COVAC plans to make recommendations twice a year. We decided on April and November for 2024.

And this is approximately one month earlier than we did in 2023 and resulted from that workshop Dr. Weir mentioned. And really, it was to balance the need for the most recent data with the timeframes needed by vaccine manufacturers to update a composition, authorize vaccines, and optimize vaccine distribution and availability. And this, of course, was a global

consideration, it wasn't just for the United States. And so then this recommendation is used by FDA committees like you and other regulatory communities to decide on what the actual vaccine will be. So to give the punchline first, and Dr. Weir already mentioned some of this stuff, but one of our objectives is not to chase variants, it's to achieve broadly cross-reactive vaccine-elicited immune response in the context of continued SARS-CoV-2 evolution. We know the virus evolves very rapidly. And what we see today is not very likely to be what's present eight months from today in the middle of winter, for example.

And really, we want to achieve this broadly cross-reactive immunity. The recommendation was that as SARS-CoV-2 virus evolution is expected to continue from the JN.1 lineage, future formulations of COVID-19 vaccines should aim to induce neutralizing antibody responses to JN.1 and its descendant lineages. One approach recommended by the ECOVAC is the use of a monovalent JN.1 lineage antigen in the vaccines.

Other formulations and or platforms can achieve robust neutralizing responses against currently circulating variants, particularly JN.1 descendant lineage can also be considered. So the nuance here is really we're looking to have antigens and new types of vaccines that would neutralize a wide variety of viruses and not just target one particular strain. Further considerations include the continued use of current monovalent XBB1-5 formulation that will offer protection given the neutralizing antibody responses to JN.1 descendant lineages and the evidence from early relative VE studies against JN.1.

However, it's expected that the ability of XBB1-5 vaccination protected against symptomatic disease may be less robust as SARS-CoV-2 virus evolution continues from the JN.1 progenitor. In accordance with WHO SAGE policy, vaccine programs should continue to use any of the WHO emergency use listed or pre-qualified COVID-19 vaccines and vaccination should

not be delayed in anticipation of access to vaccines with an updated composition. WHO stresses the importance of access to and equity in the use of all available COVID-19 vaccines.

All right. So we met as a group. We had eight meetings leading up to the final recommendation meeting, which occurred on the 15th to 16th of April, so almost two months ago now. And we reviewed this data, which is very similar to the data reviewed by this committee, so I won't walk you through all the words, but we look at the genetic evolution of the virus. That's one of many components. Antigenic characterization and immunogenicity and vaccine effectiveness play huge roles. And then immune responses to infection with currently circulating variants as kind of a hint as to what a vaccine might be like, as well as, very importantly, preliminary preclinical and clinical immunogenicity data on potential new candidates. So this slide is a phylogeny that really illustrates an overview of the evolution of the virus. So down in the left corner here, we have the index viruses, and then you may see some familiar names when we had epidemics of alpha and delta, for example, and so some evolution of the virus genetically. And then the big jump was into the Omicron lineages, and here we have the split between BA1 and BA2 and BA5, et cetera. And since that Omicron jump, everything that has occurred has been an Omicron-related virus derived from originally BA1, but most everything now is derived from BA2. The arrows indicate where previous vaccines sat, the original vaccine against the index virus, the updated bivalent vaccine in June of 2022 recommendation.

It was either a BA1 bivalent or a BA5 bivalent. And then the more recent XBB monovalent vaccine from May of 2023 recommendation and the April JN.1 recommendation from the TAGCOAT BAC committee. So you can see where all those viruses sit within the phylogeny. If I blow up the recent phylogeny, one thing that was clear was parallel evolution at

particular sites such as 346 and 456. Dr. Thornburg did a nice job covering this as well, but it's not new. We saw this with XBB-descendant lineage viruses.

Almost all of had the 346T substitution, so an arginine to a threonine. But then some of them also acquired the phenylalanine to leucine substitution at 456. And we call this parallel evolution because different parts of the phylogeny are simultaneously evolving this, so it's coming from different progenitors, and that really indicates selective advantage of those substitutions. And we'll delve into that a little bit, and KP2 is an example of something with 346T and 456L.

Overall, this was our data that we were looking at at the time, so it's a little old now, but as of March 2024, almost everything circulating was JN.1 clade virus, and this really hasn't changed. It's increased in proportion. And JN.1 clade variants continue to displace existing XBB clade variants, and we haven't seen globally any XBB-derived variants on the increase.

Dr. Thornburg covered this. I'm not going to go into too much detail, but I want to make, I guess, a couple of points. This is now showing the different vaccine components, so XBB15 versus JN.1, and one, you can see all these differences. This is a trimer, so the spike is a homotrimer. It has three monomers, and one of these monomers is colored here.

And so you can see the different domains are colored differently. And this monomer that's colored is actually shown with the RBD, which is this red and green portion, which is the receptor binding motif within the RBD, is in the up position on this monomer and the down position on the other monomers. And so we know this RBD actually moves around, and the molecule isn't perfectly static.

Another point I wanted to make was the big difference between JN.1, the only difference in the spike between JN.1 and BA2.86 was the L455S change, so right next to 456. And then

Natalie already commented on the differences between KP2 and some of the other variants, the progeny variants from JN.1 are just a few amino acids.

So I want to spend a little bit of time on this cartography. This is a lot of data summarized through data visualization using cartographs. So I know some of you are experts in this and others, it may be a little bit new to, and we have a public forum, so I'm going to describe it a little bit. Each of these squares in the background represents a two-fold difference between the things being analyzed. And the index viruses are sitting here where the D614G variant is. That was the first major variant of SARS coronavirus 2, and it really didn't have an antigenic impact on the virus. Okay, so that kind of orients you to, and the viruses are circles, serum generated from those viruses are squares.

And so this cartograph is from mouse sera, where the mice were immunized with two doses of 10 micrograms of spike mRNA vaccine for the various things listed, such as BA1, wild type, etc. And so then what you can see is each square represents two-fold. Things that are within four-fold of each other generally are antigenically alike. And so you can start to see that XBB1.5 and BA286 lineages form antigenically related clusters.

So for example, this is the XBB1.5 cluster in the southern portion here, where you have XBB1.5 and EG5 really on top of each other. EG5 had the 456 L substitution, and all of them have the 346 T substitution. Whereas the BA286 and JN.1 clade variants are over here to the east. And many-fold difference from each other, generally greater than 30-fold difference, 32-fold or at least 16-fold differences between these two. And so again, you can see these all cluster together.

The 346 T and 456 L, that represents a KP2-like virus. And then the KP3-like virus is just off to the north here. Again, probably within two-fold of these viruses. The JN.1 sera is shown in

these orange squares, so two doses of JN.1. And so that's showing you kind of where the sera sits and what it would neutralize. And so the sera are listed in the squares, and so you can get a sense of the overlap between the sera and the various viruses. The best way to understand antigenic distance is with this naive type model. Of course, we can't do that in humans anymore. Now, there's a couple of other take-homes that may help you understand the difference between these viruses and what these squares mean.

So again, focusing on the index virus, you can see SARS-1 up here in the north. This was tested in this study, and this was a virus that jumped from bats into palm civet cats and raccoon dogs in live animal markets in 2003 and 2004. And then it jumped from those animals into humans and caused an outbreak, a global outbreak of more than 8,000 cases.

And so to give you a sense of how antigenically evolved SARS-2 has become, this distance is actually looking shorter than the distance to JN.1 or the XBB viruses, and it's a good example of why we need to update the vaccine. And genetics isn't the only thing. BA287.1, this is a virus that evolved very different amino acid changes than BA286 had, but it really never went anywhere. About nine cases were identified. And you can see partly why is because it really sits, it's pretty well neutralized even by early progenitor serum and these other sera as well. So it kind of sits in the middle and it doesn't, it's not antigenically advanced, even though it has a lot of genetic changes.

So XBB1.5, the take-home is XBB1.5 and JN.1 are antigenically very different from each other, and each of these groups is forming very closely related antigenic clusters. Now there's very few naive humans out there, but this – Dr. Cao's group also was able to find some naive humans and do a similar kind of analysis. And while the orientation is different, the relative differences between the index viruses such as 614G, the JN.1 clusters and the XBB clusters are

similar. So we can see even in the humans, in naive humans, this recapitulates a little bit that mouse model. Now in most of us, we've had prior exposures.

And so this is important because it's looking at participants from the United States, and we're looking at a sera collected prior to vaccination in green and post-vaccination in pink. And I'll just focus on this top panel to start with, and on the left-hand side with the neutralization titer. And so you can see folks that had just the primary, the vaccine of XBB1.5. They start with a fairly high titer to the ancestral.

This is a little bit of what Dr. Perlman was alluding to, I think. They start with a little high titer of the ancestral and the BA5, but it drops considerably to XBB1.5, so a 27-fold reduction. And then when you, well, actually, it drops considerably to BA5. That's not the reduction. But when you vaccinate, you get a 27-fold increase, and you get titers in the thousands against XBB1.5. And then as I mentioned, EG5 displaced, or Dr. Thornburg mentioned, EG5 displaced XBB1.5, and that had this 456L substitution. You can see it's still, the vaccine still neutralized that virus pretty well.

And we do see a reduction to JN.1. So while it's not as significant as you see in the naive model, it does point to the fact that JN.1 does escape immunity, even that immunity elicited by the previous vaccine, XBB1.5. Now, in people that had been also infected by a BA virus, like BA2 or BA5, their starting titer is higher. But when you vaccinate them, they get boosted.

Again, it's just not as high of a boost. But you end up with a very good geometric mean titer. It's a very consistent pattern, and you do see some reduction to JN.1. And the same is true for those that were XBB1.5 vaccinated and had previously been infected by an XBB virus. Again, what you're seeing there is a higher starting titer to XBB that's boosted to a good high titer, but it's just not as a large fold increase. It's only 5.5 versus 27. And in each of these cases,

you can see a back boost into the past of cross-reactive antibodies that are generated by the response to the new antigen. So it's a lot of data. I just want to be sure I covered all of that.

Now, in contrast to the United States, this is folks from China, and it's again from Dr. Cao's lab. So it's a very complicated set of data, but I'm going to walk us through it. We have XBB infections alone in this top panel.

So these are people that were naive, and in part because of the zero COVID policy, really had never seen even the index virus and caught XBB1 infections. There were only 11 folks, but you can see they have the highest titer to XBB1. It decreases a little bit into HK3.1, which has 456L substitution and others, and then decreases more substantially into BA5, and you have no reactivity back into D614G.

So this contrasts what you see in most people that have had exposure or prior exposure to index viruses through vaccination or infections. Now, a naive JN.1 infection looks like this, where you have good cross-reactivity to JN.1, BA286, and the various variants of JN.1 that are coming out. And so this includes JN.1 with 456L, a KP2-like virus here, which is JN.1 with 346T and 456L.

So to answer one of the earliest questions, this data might be considered non-clinical human data, because we're just looking at the effect of infections, and there's a lot of uncontrolled issues here. But the take-home is JN.1 gives you about a 200 titer. You get a subtle reduction into the JN.1 with the 456L and 346T substitution, down to 140, and almost twofold into the KP3 virus.

Now, if we switch gears a little bit here and talk about people that had been infected by a BA5 or BF7-like virus, so that's related to BA5, and then followed by an XBB infection, and we look at their titer against JN.1, it's only 121. They have a good titer against XBB1.5, like of

1,000. So a pretty substantial reduction. And it's further reduced as you add additional changes, stays less than twofold with the KP2, and goes outside of twofold with KP3. Now, if they're infected by JN.1, it gives you a higher titer to JN.1, and a little bit, it's a similar pattern as you saw before, but everything's a little bit higher titer, with KP3 being the most reduced. Now, here is people that are a little bit more like our population, in that they have titer to the early virus, but this is primarily from vaccination. And then they were infected by so BA5 and XBB, so have a little bit more history, immune history, and then what their titer is to JN.1, 66, and again, a similar pattern of fall off as you get to these more, the newer variants, like KP2 and KP3, again, within twofold. And when you get a JN.1 infection, this boosts it up to 389 from its starting point. And again, you get a similar pattern of reduction as we add to the variants.

There are some confounders here I want to point out. For the JN.1 versus the XBB infections, there's a longer time point between their prior infections, and this is partly because of, you know, the chronology of events of variant evolution, and there's not much we can do about that. Okay, Dr. Gelles already covered a lot of this, so I won't belabor it. We looked at a lot of BE estimates. I'm only showing you one. We look at a global situation, and so here we're looking at the top panel against hospitalization, symptomatic disease, hospitalization, and severe disease. The middle panel is symptomatic disease, and bottom panel is the hardest to from infection. And then the color coding goes XBB-like viruses as blue, and most of these are EG5 or further evolved viruses that have 456L substitution, and JN.1 in red. And what you can see is against severe disease and hospitalization, we do see a kind of a consistent pattern with the point estimates being reduced to JN.1 from that of XBB. However, as Dr. Gillis mentioned, and this is true for symptomatic disease as well as infection, so we see the same pattern from different studies in different parts of the world. However, in all cases, the confidence intervals overlap,

and so it makes—that's not a statistically significant reduction in point estimates, but we do see that consistent trend.

And as Dr. Monto already mentioned, this is confounded by the chronology of events. As you get variant evolution, more time goes by since people have been vaccinated, and so this can also negatively impact your BE, of course, because of waning immunity. I kind of think about it like this, you know, antigenic evolution really just speeds up waning immunity.

So, in summary, the genetic analysis showed that as of April, all the SARS coronavirus sequences publicly available were derived from JN.1. JN.1-derived variants, there's a lot of them, and they've independently evolved changes in protein at epitopes involving amino acid residues 346 or 456. Substitutions of these residues have been identified in previous SARS variants. R346T in BQ1, which was a BA5 descendant, and in XBB. F456L in EG5, so EG5 included both 346T and F456L, for example, and are within epitopes known to be targeted by neutralizing antibodies. The displacement of XBB lineage variants by JN.1-derived variants shows that it's likely that in the near term, future circulating viruses will be derived from JN.1.

From an antigenic characterization standpoint, in naive animal models and in human sera, XBB1.5 and JN.1 viruses are antigenically very distinct from each other. They form distinct antigenic clusters of antigenically closely related variants. Naive animal JN.1 antisera reacts well with many co-circulating JN.1 progeny variants.

In non-naive animals and humans, so non-naive animals are sequentially immunized animals, and I didn't show you data from that, but you might see some a little later today. It's done to mimic our immune history. Monovalent XBB1.5 vaccination sera neutralized XBB1.5 in the progeny, as well as BA286 and JN.1 lineage progeny variants.

So, despite this big antigenic difference, when you have an immune history, you get a lot more cross-reaction into the JN.1 progeny. However, the neutralization titers against JN.1 in published and unpublished studies were typically lower. This was two to five-fold than those against the homologous XBB1.5 immunizing antigen. And additionally, there are small reductions in cross-neutralization of JN.1 progeny with 456L or 346T substitutions in S, and similar reductions were also observed in very few studies where KP3 representatives were included, and these have the 456L and Q493E, which we haven't seen a change at that position since the original Omicron emerged. So, with VE studies that focused on monovalent XBB1.5 vaccine during periods of XBB descendant lineage circulation, it is a high VE within the first three months after vaccination, but protection against symptomatic disease is lower. There are fewer studies with relative VE for the monovalent XBB1.5 vaccines during periods of JN.1 descendant lineage circulation, and they show additional protection offered during the first three months after vaccination, but point towards a slight reduction in VE as compared to VE against the XBB1 lineage variants for protection against both symptomatic disease and severe disease, and the observations are consistent with the reduction of neutralizing titers.

Preclinical data shared confidentially with TadcoVac by manufacturers indicated that immunization of naive mice as well as mice previously immunized with representative SARS-CoV-2 variants with monovalent JN.1 vaccine candidates elicits higher neutralizing antibody titers to JN.1 and its emerging descendants as compared to responses elicited by currently approved vaccines. In one immunogenicity study in humans using a monovalent JN.1 containing vaccine candidate suggests that a JN.1 vaccine antigen is likely to produce higher neutralizing antibodies to JN.1 as well as emerging descendants such as KP2 than an XBB1.5 related antigen.

So, finally, I wanted to just give you a little bit about the considerations. We did talk a lot about what specific antigen, just like this committee is doing, to include in the vaccine. And of the potential candidates, we only had immunogenicity data from JN.1 at the time of the TadcoVac analysis. This included naive and sequentially immunized animal models. Post-infection and post-vaccination human sera reacted well with JN.1 and its variant, descendant variants, and JN.1 is genetically and antigenically central. So, emerging variants react well with JN.1 and sera and typically are within two-fold. Now, our committee, of course, is fairly risk-averse in making these kinds of decisions.

So, you really want to have this kind of immunogenicity data. So, progeny variants, and part of this is, I'm going to tell you a little bit, part of this is the progeny variants can become antigenically farther apart from each other than a JN.1, than they are from their parent. And so, I've depicted that here.

This is an artistic illustration of cartography. It's not really cartography, but it's to help visualize this point. So, JN.1 might be sitting here. We have KP2 within two-fold of it, KP3 a little bit more than two-fold of it, and JN.1.3, which has very different substitutions, 444 and 453, also a little bit, you know, around two-fold different than JN.1. Now, each of them is evolving in a multidimensional way. It's not, they're not evolving in two dimensions.

The antigenic space is really the multidimensional space, and they're evolving away from prior existing immunity from previous infections. And so, what can happen is they can evolve away from, you know, earlier viruses, but they can become farther apart from each other. So, in this depiction, KP3 and KP2 might be four-fold apart, whereas KP3 and JN.1 are only two-fold apart. And so, parsing this kind of information is very difficult and, of course, very theoretical. The evolution may drive things together, such as parallel evolution. And so, this arc is meant to

say, well, KP3 may move this way, and KP2 may move this way, and they may become very close together, and this is the difficulty.

And this is why cross-reactivity with human sera against emerging variants, such as KP2, is really needed. It's unknown in this situation. It may provide better reactivity with KP2 or its descendants or have greater breadth, but it may also not provide as much breadth, reduce reactivity to other JN.1 variants. And some of this is the evolution may also be driven by other fitness advantages that could negatively impact vaccine immunogenicity, and these include spike stability, RBD positions, human ACE2 binding. And the final consideration, of course, is earlier vaccine availability from multiple vaccine platforms is critically important. So, what we've seen since then is the continued diversification of JN.1.

That's illustrated here. We have lots of amino acid substitutions happening. There are a few countries with increasing SARS activity.

This is Thailand, where JN.1 predominates so far with the data that we have. Singapore, where JN.1 and KP2 slash KP1 are co-circulating. New Zealand, where JN.1 is circulating and KP3 is, it's more than KP3, but KP3 is on the rise. We've seen increases in KP2 and particularly KP3 as of week 18. So, to give you a sense, our committee met in middle of April. KP3 viruses are these blue viruses like this.

There are really very few viruses at that time point, but now the global prevalence of KP2 is around 15 percent and the global prevalence of KP3 is around 16 percent, and this can be broken down by region. KP2 is about 17 percent in Europe, 14 percent in the Pacific, whereas KP3 is higher in the Western Pacific, around 20 percent, 17 percent in the Americas, and 13 percent or so in Europe. And these are the limitations.

We continue to have persistent and increasing gaps in genetic surveillance. This is becoming more and more of a problem. The trajectory of SARS evolution suggests JN.1 is the progenitor of things in the near term, but timing and genetic characteristics and public health impacts of newly emerging future variants remain unknown.

Data on immune responses following XBB and JN.1, as well as others, are largely restricted to neutralizing antibodies. Immunogenicity data against currently circulating SARS variants are not available for all COVID-19 vaccine platforms. An estimated relative VE against recently circulating SARS variants, including XBB and JN.1 lineages, are limited in terms of the number of studies, the geographic diversity, vaccine platforms evaluated, populations assessed, duration of follow-up, and comparative estimates for non-available vaccines versus other formulations.

I'd like to end by acknowledging all the members of the committee that worked very hard to look at all this data. Thanks.

Dr. Monto: Thank you, Dr. Wentworth, for your usual very clear and comprehensive report of a lot of data. We are running short on time. We're going to have to cut into our break no matter what. So, only the most important or precise questions right now. Dr. Levy.

Dr. Levy: Thank you for a great presentation, Dr. Wentworth. You've raised this briefly in your conclusions. Other types of immunogenicity data are limited. We've discussed this previously on this committee. Antibodies are easier to measure. They're quantitative. They're important, so I get it. But in my personal opinion, we continue to shortchange cell-mediated immunity as an important parameter, and given the sophistication across the world and the ability to measure cell-mediated immunity, in brief, what are the barriers and what can we do to get better

information in that regard and consider it, because it could be important to the protection afforded by the vaccines. Thank you.

Dr. Wentworth: Well, thank you, Dr. Levy. I think, you know, you've raised this point. It's a very good point. I'm going to make a couple of comments in response. So, there's some technical limitations, and there's just not as high throughput, so, that's one issue. But the other thing is where the virus is evolving. So, escape from neutralization is the primary driver of the virus evolution in the war against our immune system.

So, that's really become clear, much more clear than it used to be. Omicron is a great example, and all the descendants since. If you look across the genome, you're not seeing all these mutations pop up everywhere.

You're seeing them in particular regions of spike, not in S2, but in S1, right? And, of course, T-cells are much smarter, right? They're designed to look across the viral proteome. And so, the impact on the T-cells of these changes in the vaccine isn't going to be as dramatic as your impact on the generation of new neutralizing antibodies, as well as affinity maturation of old memory antibodies that would better bind these new variants, right? And so, part of it is, if you keep up with the neutralizing antibodies, you automatically keep up with T-cell epitopes because they're a little bit more, if you excuse the pun, they're immune to some of these little variant wobbles because they break the proteins up into very small bits, as you know, but I'm just making that point. And so, there's lots of the proteome of the virus, particularly if you've infected prior, that you have great cytotoxic T-cell immunity to.

And T-cell immunity isn't going to protect you from infection. It's likely not going to protect you from the initial parts of symptomatic disease. It's going to help you in clearance of the virus and protect you from severe disease. And so, it's important to boost that, but it is longer

lasting than neutralizing antibodies are. So, long-winded, but really the primary driver of evolution in the virus, you can clearly see it, is escape from neutralization. If you look at polyclonal sera, it really reacts well in cross. And so, that's simple to measure.

Dr. Levy: Okay, thank you.

Dr. Monto: Dr. Gans.

Dr. Gans: Thank you so much. That was wonderful. Very quickly, since we can't really predict out of the J1 lineage and the KPs 1 and 2, if it's going to be convergent or divergent in terms of where we're going in the future, we can't predict where sublineages are going, if you were to make a proposal on how to diversify the immune response to the broadest, why would it not include either both of those lineages in case they go divergent, sublineages to go divergent and get us the best protection? So, I'm just wondering what you would opine on including the, any form of sublineages in terms of what that would do for our immune response.

Dr. Wentworth: Great idea, and it deserves consideration by your committee. You know, we already made our recommendations in the static point in time, you know, one and a half to two months ago. So, we're looking at a little different situation. But I think what I tried to touch upon, the one slide that's different in this deck is from what I gave to regulatory community and vaccine manufacturers a month and a half ago was this slide comparing, you know, JN.1 versus KP2 as choices. You could kind of consider KP3 in there as well. It's really challenging, right, because I think the key is to have antisera to those viruses, and ideally you want human antisera to those viruses to better understand exactly what would happen.

And as Dr. Perlman mentioned, really the vast majority of the response is driven by cross-reactive B-cell memory responses that are to the new antigen. They're not all to the old antigen. There are things that cross-react with the new antigen, and JN.1, we do have data for

that from both animal models and humans, whereas as a committee, we didn't have any data on KP2, and what I was trying to get at with that fake cartography was KP2 may be better, but it could also be worse, right? And the reason it could be worse is multifactorial.

It could not create as high a titer when you immunize. That's one of the issues, right? Or it creates a very monospecific titer where it really neutralizes KP2 well but doesn't neutralize other variants as well. And this we saw with XBB15 had a broader cross-reactivity pattern than XBB1, for example, last year, and part of the reason XBB15 was kind of narrowed down as the monovalent recommended by the WHO committee.

So kind of looking at the prior history, the limited history we have, that's the challenge, and whether or not you have artificial intelligence, there are efforts in that space, but you really need the data to help inform either the human intelligence or the artificial intelligence, which is antisera to those newest variants, which when you have a variant like KP3 that just popped up, it takes a month to make antisera. So we're always going to be in that situation of only knowing what we know now. And I would just finalize by saying we've really seen KP3 increase a lot, and that 493 substitution from a glutamine to a glutamic acid is probably more impactful than the 456L substitution. So I want to make sure the serum neutralizes within fourfold the variants that I know are important, which are KP2 and KP3.

Dr. Monto: Thank you so much, Dr. Wentworth. I think although some people say it's not flu, we're beginning to get into the same situation with the tag recommendations, which allow some flexibility and talk about lineages rather than a specific variant, because there are other considerations. We're going to have to cut our breakdown to 10 minutes, so we will reconvene at 11 o'clock Eastern. And we're on break now until 11 o'clock.

**Moderna Presentation: Moderna COVID-19 Vaccines Update**

Dr. Monto: Okay, welcome back to the 185th meeting of the Vaccines and Advisory Committee meeting. We're next going to hear from the three manufacturers, first Moderna, then Pfizer, and then Novavax. Each has 20 minutes to present, so please keep to time because we'd like to have a little time for questions at the end of your presentation. So next, we are going to hear from Moderna, Dr. Frances Priddy, over to you.

Dr. Priddy: Thank you. Good morning, my name is Fran Priddy, and I'm Executive Director for Clinical Development of COVID-19 Vaccines at Moderna. We are pleased to share with the committee today an update on COVID-19 vaccine development at Moderna and data relevant for the 2024-2025 season. Moderna continues to monitor emerging SARS-CoV-2 variants to inform development and evaluation of updated COVID-19 vaccines. We're committed to generating preclinical data to share with agencies worldwide and inform vaccine update decision making.

We continue to assess clinical samples for cross-neutralization of future variants, and this fall we will conduct a small open-label clinical trial if an updated vaccine is authorized. Additionally, we maintain manufacturing readiness to respond rapidly and supply new COVID-19 vaccines as recommended. Today, we will review safety surveillance data and the results of our effectiveness study of the XBB-1.5 vaccine, which complements the work that others have presented today.

We will also show you the cross-neutralization ability of the XBB-1.5 vaccine for the JN.1 family of variants. Finally, we have developed investigational JN.1 and KP2 containing vaccines, and we'll share preclinical data on this later in the presentation. Let me begin with a brief update on XBB-1.5 vaccine use and safety surveillance over the past season.

As of March of this year, we estimate that 45 million doses of Moderna XBB-1.5 vaccine have been administered. Our safety surveillance has not identified any new safety concerns, and

thus the favorable benefit-risk profile of our vaccine is unchanged. Now I will share interim data on the effectiveness of the XBB-1.5 vaccine in an ongoing study in adults in the United States.

This is an observational retrospective study, which uses the Veridigm electronic health record database linked to Komodo health care claims. This is an integrated data set which includes more than 172 million adults in the U.S. The study has a matched cohort design with two groups, shown here, each including approximately 860,000 subjects. The exposed group are those who received the Moderna 2023-2024 vaccine, and the unexposed are those who did not receive this vaccine.

These participants were matched on the variables shown here on the right, including prior receipt of a bivalent VA45 vaccine. We assessed vaccine effectiveness for both COVID-19-related hospitalizations and medically attended COVID-19. Medically attended COVID-19 included settings such as ER visits, urgent care visits, office visits, and lab results. Vaccine use was captured during the end of 2023, period when XBB lineage variants were predominant, and the study had a median of 63 days follow-up after vaccination. Overall, the two groups in the study were well-balanced with the mean age of 63 years, 71% had a history of prior bivalent COVID-19 vaccination, and over 80% in both groups had a history of any prior COVID-19 vaccination. Moving now to the vaccine effectiveness results.

Recipients of the Moderna XBB15 vaccine demonstrated a vaccine effectiveness of 60% against COVID-19-related hospitalizations, compared to those who had not received an updated vaccine. Effectiveness against medically attended COVID-19, shown on the right, was 33%. Effectiveness for each endpoint was similar across the subpopulations shown below.

These data confirm the Moderna XBB15 vaccine provides protection against COVID-19-related hospitalization and medically attended COVID-19, demonstrating the benefit afforded by

updated COVID-19 vaccination. I will now share clinical data on the ability of the currently approved Moderna XBB15 vaccine to cross-neutralize emerging variants from the JN.1 lineage, which are currently dominant globally, as described earlier. We assessed 49 adults who were previously vaccinated with four doses of Moderna vaccine, including the bivalent BA45 vaccine.

These adults then received the Moderna XBB15 vaccine. 67% had evidence of prior SARS-CoV-2 infection prior to the fifth dose. Serum obtained at day 29 and six months after vaccination were tested for neutralization in a pseudovirus assay. Here are the day 29 neutralizing antibody results. The titers shown here are against the XBB15 variant in the vaccine. Hash bars show the pre-booster titers and the solid bars show the day 29 neutralization results.

As shared with the committee last year, robust neutralizing responses are induced to the XBB15 variant. Now shown on the right are cross-neutralization titers against three viruses from a selection of JN.1 family of variants. At day 29, neutralizing responses to these viruses are also demonstrated. However, the GMTs labeled above each bar in black text are five to 10 times lower than the titer achieved against XBB15 at day 29. These data suggest that JN.1 sub-variant viruses have evolved to significantly evade immunity provided by the currently approved XBB15 vaccine.

Now here's the same slide with the six-month data added in the brown to the right for each variant. Neutralizing antibody responses to all strains were demonstrated through six months after XBB15 vaccination. Titers against the variant in the vaccine shown on the left were durable and remained five-fold higher than pre-boost values at six months. In contrast, responses to the newer JN.1 variants shown on the right were considerably lower at six months than those for the variant in the vaccine.

These data demonstrate durability of immune responses to the variant in the vaccine after XBB15 vaccination. However, the reduced responses to newer JN.1 family variants, particularly over time, suggest a vaccine update may be indicated. I will now turn the presentation over to my colleague, Dr. Edwards, to share data on variant monitoring and pre-clinical assessment of new vaccines.

Dr. Edwards: Thank you, Dr. Priddy. My name is Darin Edwards, and I am Executive Director, Program Leader of COVID-19 Vaccines at Moderna. Moderna has continued to follow the evolution of the SARS-CoV-2 virus, and our ongoing genomic surveillance have enabled us to identify key new variants early.

JN.1 and its sub-lineages comprise approximately 94 percent of the collected globally currently. While JN.1 has recently decreased in frequency, several JN.1 sub-variants, characterized by two or more mutations in the receptor-binding domain of the spike protein, are now predominant. KP2 has recently become the most commonly sequenced variant in several regions, including the U.S. and the U.K. KP3 has also increased more recently and has become now dominant in Canada, Australia, and other countries.

As I will show, our current data suggests that a JN.1 or KP2 new variant vaccine will protect against JN.1, KP2, KP3, and other JN.1 sub-variants that are now co-circulating. Somewhat redundant to earlier presentations, but here is a comparison of the antigenic differences between JN.1 and XBB1.5, the variant in the currently authorized vaccine. The circles in these Venn diagrams show the total number of mutations for JN.1 and XBB1.5 versus the ancestral virus.

JN.1 differs significantly from XBB1.5, with 29 unique mutations in JN.1 and 11 in XBB1.5, for a total difference of 40 mutations between these two variants. This level of

antigenic change, especially in key sites of known neutralization in the receptor binding domain and the N-terminal domain, tell us that the JN.1 lineage has evolved to significantly evade immunity provided by prior Omicron infection or the currently authorized XBB1.5 booster. Here we see the antigenic differences between JN.1, KP2, and KP3.

Starting on the left, comparisons are made between JN.1 versus KP2, JN.1 versus KP3, and KP2 versus KP3. Limited antigenic differences are noted between these three variants, with only two or three mutations in the spike protein differentiating these variants. This analysis suggests that a JN.1 or KP2 new variant vaccine is likely to cross-neutralize currently circulating JN subvariants, regardless of which is selected as the updated 2024-2025 COVID vaccine.

And now I would like to walk you through our preclinical studies of our investigational JN.1 and KP2 new variant vaccines. We have developed these vaccines and have evaluated each in preclinical studies versus the currently licensed XBB1.5 monovalent vaccine. Both primary two-dose vaccination studies as well as booster studies have been completed for the JN.1 vaccine, and booster studies have been completed for the KP2 vaccine.

The primary series was conducted in naive mice who received a two-dose regimen of either the JN.1 vaccine or the licensed XBB1.5 vaccine. Assessment of a primary series of the KP2 new variant vaccine is still ongoing. The booster vaccination was assessed in mice previously immunized with the two-dose series of our original vaccine, mRNA-1273, and subsequently received either one dose of the JN.1 vaccine, one dose of the KP2 vaccine, or one dose of the licensed XBB1.5 vaccine.

First, I'll show the neutralization titers in mice vaccinated with a primary two-dose series of either the XBB1.5 vaccine or the JN.1 vaccine. CR were obtained 14 days after the completion of the primary series. Here on the left are the neutralization results for XBB1.5

vaccine against XBB1.5, JN.1, and four JN.1 sub-variants, including KP2. We saw high levels of neutralization against the XBB1.5 virus, but limited neutralization of the JN.1 variants. In contrast, the JN.1 vaccine on the right demonstrated high levels of neutralization against all five JN variants, but low levels of neutralization against XBB1.5. So the JN.1 vaccine not only neutralized JN.1, but also cross-neutralized sub-variants of JN.1.

Next, I will describe the neutralization titers in our booster study comparing the currently licensed XBB1.5 vaccine to the investigational JN.1 vaccine. Neutralization was assessed prior to the booster dose, shown with the hashed lines, and after, shown with the solid colors. The fold increase in titers measured after the boost compared to the pre-boost titer is listed below the graphs. The JN.1 vaccine, shown on the right, increased neutralization against JN.1 sub-lineage viruses to levels higher than the XBB1.5 booster, shown on the left.

These data show that a JN.1-containing vaccine neutralizes JN.1 and cross-neutralizes multiple JN.1 sub-variants, including KP2. Next, I will describe the neutralization titers in our booster study comparing the currently licensed XBB1.5 vaccine to the investigational KP2 vaccine. The KP2 vaccine, shown in green, increased neutralization against JN.1 sub-lineage viruses to levels higher than the XBB1.5 booster, shown in orange.

These data show that a KP2-containing vaccine neutralizes KP2 and cross-neutralizes JN.1 and other circulating JN.1 sub-variants, including KP3. In summary, our preclinical results suggest that both a JN.1 and a KP2 new variant vaccine cross-neutralizes JN.1, KP2, KP3, and other currently circulating JN sub-variants. Based on the FDA's recommendation, Moderna is prepared to submit a JN.1 or KP2 new variant vaccine dossier for approval and is ready to supply the U.S. market with either vaccine composition by mid-August.

So, with that, I would like to summarize the data we have shown you today. The currently licensed 2023-2024 XBB1.5 vaccine was effective against COVID-19-related hospitalizations and medically attended COVID during the period prior to JN.1. This was shown in our effectiveness study and in the data presented earlier today by the CDC. We have not identified any new safety signals with this vaccine. The vaccine continues to be well-tolerated and performs similarly to the original COVID-19 vaccine and the other booster vaccines authorized by regulatory agencies over the last few years. Preclinical data suggests that either a JN.1 or KP2 new variant vaccine cross-neutralizes JN.1 and currently circulating JN sub-variants.

We will conduct a small clinical study post-licensure of the vaccine selected for the fall to help address whether there will need to be future changes in vaccine composition. And we confirm that Moderna is prepared to provide adequate supply of a new variant-containing vaccine by mid-August based on the recommendation made by the FDA. Thank you very much to the committee for the opportunity to present today. We also thank our investigators, study site personnel, lab personnel, and all the individuals who participated in our clinical trials. And we will be happy to address any questions.

Dr. Monto: We have time for a few questions. Dr. Perlman.

Dr. Perlman: Thank you for the presentations. Those data were really interesting. So, when you do these assays, when you look at either the human data or the mouse data, do you ever do assays where you absorb the virus, remove all the cross-reactive antibody or cross-reactive to the ancestral strain and then see what fraction of the total antibody is newly induced antibody against the variant that you've added to the vaccine?

Dr. Priddy: I'll ask my colleague, Dr. Edwards, to take that question.

Dr. Edwards: Yes, Dr. Perlman, thank you for the question. So, we have actually conducted such an experiment recently using not only animal sera, but also human sera. It's a collaborative study that we conducted with Mike Diamond's laboratory at Washington University and also with the Vaccine Research Center at the NIH. It was really designed to assess the level of immune imprinting or antigenic specificity of the antibodies in the B cells that we elicit after boosters. And this study was recently published. What I found is that the antibody response to, at the time, Omicron-based boosters, both XBB and the BA45 bivalent, does show imprinting by immunizations with the historical mRNA-1273 vaccines. But they actually found that the outcome may be beneficial as it drives expansion, not only of cross-neutralizing antibodies that inhibit infection of these emerging SARS-CoV-2 variants, but also even found that it drives cross-neutralization of even more distantly related SARS-CoV-2 viruses. So, I hope that answers your question.

Dr. Perlman: Thank you.

Dr. Monto: Thank you. Dr. Meyer.

Dr. Meyer: Thank you so much for that presentation. That was very helpful. I have two questions. My first question relates to the mice data that look at neutralizing antibodies after either JN.1 or KP2 vaccine. It looks like the antibody titers after JN.1 are a little bit higher than after KP2 vaccination, but they're very similar. So, I just want to confirm, is your interpretation of the data that they equally perform, or do you think that there is some slight advantage to the JN.1 vaccine? That's my first question.

Dr. Edwards: Yeah, no, thank you for that question. I'm showing back the JN.1 data, and then in just a second, I'll share the KP2 once again. That is our interpretation. It's very difficult to see significant differences in the performance of either the JN.1 or the KP2 vaccine in this type of

model, this boosting model, this model of boosting with these updated vaccines. So, yes, I do confirm that's our interpretation. Great.

Dr. Meyer: Thank you so much. My second question is, it was helpful to see that Moderna plans to have supply for either JN.1 or KP2 by mid-August. My question for that is the kind of volume or doses available at the start, because I think from a program perspective, you know, it's helpful to have as much supply available at the start when people are seeking the vaccination versus like a trickle out over time. So, my question is, for either of those vaccines, would you expect a difference in terms of the amount of vaccine available in mid-August, and kind of if there's any differences, what would be the magnitude of that?

Dr. Edwards: So, we are still in negotiations with some key retailers and pharmacy chains for contracts for the fall. That said, our projections are that either vaccine, we will have sufficient supply to supply not only at the initiation of vaccination campaigns, but throughout the season for either vaccine composition.

Dr. Monto: Thank you. Final question, Dr. Gans.

Dr. Gans: Thank you very much. I had two very quick questions. The serology data that you presented on the pre-vaccine where they boosted in the human data, I'm imagining those data, I'm interested in the pre-vaccine, they were inclusive, did you exclude people who had natural disease, because it looked like there was no increase in the, there was no clear serologic evidence of protection that then obviously needed boosting. So, if you could just say how those individuals were kind of tested for natural disease. And then I'm wondering if there's a way to put the J1 and KP2 data on the same slide so that we could see the boosting of those, because it's really not necessarily the number of mutations, while that's important, it's really the kind of mutations. And so, it would be nice to see those side by side, actually.

Dr. Edwards: And for the first question, I will pass it back to my colleague, Dr. Priddy.

Dr. Priddy: Thank you, Dr. Edwards. In the clinical data that I showed today on the study, the subjects all had a history of prior vaccination. And that study enrolled subjects regardless of their prior infection history. We did evaluate the enrollment prior to the booster, so we know what the infection history was. And as I mentioned, it was about 60% of subjects in this cohort had a history of prior infection. We do have the data, which I can show the immunology results.

These are the breakout of the immunology results I showed after the XBB1.5 vaccination. This is broken out by subjects with and without prior infection. Just to give you a sense, the responses to the XBB1.5 variant in the vaccine are shown on the left, newer variants on the right. And basically, we see no difference between subjects with and without prior infection in this small cohort. Dr. Edwards?

Dr. Gans: Thank you.

Dr. Edwards: And for your second comment, unfortunately, we don't have a slide that shows the KP2 and JN.1 vaccine results side by side, but the slides that we presented are posted on the website. And hopefully, that allows for an easy interpretation. Oh, sorry. I'm seeing that we actually do have that. No, sorry, we don't. We can try to put that together. And if you have the same question after the break, we'll have that available.

**Pfizer presentation: 2024-2025 COVID-19 Vaccine Formula: Pfizer/BioNTech Clinical and Preclinical Supportive Data**

Dr. Monto: Thank you very much. We're moving on to the presentation from Pfizer. And Dr. Modjarrad will be presenting to us. Please keep the time so we can have some questions. Thank you.

Dr. Modjarrad: Thank you. Good morning. My name is Kayvon Modjarrad. I'm the Executive Director of Viral Vaccines within Vaccines Research and Development at Pfizer. On behalf of

Pfizer and BioNTech, I will present the summary overview of data that we've generated to support the selection of the composition for the 2024-25 COVID-19 vaccine formula. First, I'll provide a focused review of our real-world effectiveness data for the 2023-24 Omicron XPB1.5 adapted vaccine, and then present a snapshot of the currently evolving SARS-CoV-2 variant landscape. I will then summarize immunogenicity data from our XPB1.5 vaccine clinical study and conclude with the preclinical evaluation of our Omicron Jane 1 lineage adapted vaccines.

It's first important to stress that although COVID-19 disease burden has decreased since it precipitated the pandemic four years ago, it remains one of the leading causes of morbidity and mortality in the U.S., still exceeding or at least matching levels observed for influenza. Data from the CDC plotted here show the total number of seasonal hospitalizations on the left and deaths on the right in the U.S. caused by influenza in green and COVID-19 in blue over each of the last few years. As you can see, COVID-19 hospitalizations in the U.S. have fallen from the initial peak of 1.9 million. However, COVID-19 still caused more than 550,000 hospitalizations and 40,000 deaths in the fall and winter months alone of this last year, a disease burden that is comparable to influenza during the same time period and to influenza in the pre-pandemic years. Vaccines therefore remain a vital public health tool to reduce the burden of COVID-19 disease, even as we transition from the pandemic to a more endemic state. In the last year, XBB1.5 vaccines have been made available to individuals six months of age and older and studies of vaccine effectiveness, which I will abbreviate as VE, indicate that the updated vaccines performed well this last fall and winter season.

In this graph, published point estimates of XBB1.5 VE are plotted over time. The blue dots represent VE against hospitalization and the purple are against less severe clinical outcomes.

The colored shading notes the period of follow-up in the studies that generated the corresponding point estimates.

During the time when XBB sublineages were dominant, captured in the green box on the left, XBB1.5 vaccines had high effectiveness, particularly against hospitalization at above 70%. As the J1 lineage emerged and its prevalence rose, depicted in the shaded red overlay and red box toward the right, XBB1.5 vaccines still provided protection, but at lower levels. As the drop in VE observed in this graph represents an ecological trend, we conducted additional studies to tease apart the impact of waning immunity from the changing variant epidemiology in individuals who received the XBB1.5 adapted Pfizer-BioNTech mRNA COVID-19 vaccine.

In two studies, one conducted in the VA health system and the other in the Kaiser Permanente network, we assessed VE after controlling for the potential impact of waning immunity by restricting the time since XBB1.5 vaccination to 60 days. Both studies used a test negative design in adults with acute respiratory infection and compared the odds of having received the Pfizer-BioNTech XBB1.5 vaccine in SARS-CoV-2 positive cases to the test negative controls. Gray and red dots respectively indicate VE against hospitalization during periods of XBB and J1 lineage dominance.

In both studies, VE was lower against J1, even after controlling for time since vaccination. Similar trends were observed for less severe clinical outcomes. Together, these data suggest that the reduced VE of XBB1.5 vaccines over the course of this last season was largely due to the rising prevalence of J1 sublineages, which have now become predominant globally. The evidence, therefore, indicates a sufficient antigenic distance of currently circulating sublineages from the XBB1.5 vaccine to justify an update to the 2024-25 COVID-19 vaccine formula. To guide considerations for the composition of that update, it's important to track the

current variant landscape and view it from the lens of last year's variant trajectories. Last year, XBB1.5, shown in the gray curve of this longitudinal prevalence plot, was falling from dominance at the time a strain recommendation was made, while related sublineages like XBB1.16 and EG51 in the light blue curves were rising, and in the case of EG51, peaking at the time the XBB1.5 adapted vaccines were approved.

Despite the decline in XBB1.5 prevalence, the XBB1.5 vaccine was very effective against drifted but related XBB sublineages, as revealed in the real-world studies shown earlier. This year, as J1 sublineages took over the epidemiologic landscape, a similar pattern emerged. J1, shown in red, has followed an arc similar to XBB1.5's trajectory last year.

Now, as the parental J1 lineage falls in prevalence, descendant sublineages compete to take its place, as we also saw among XBB sublineages last year. Among these are the sublineages that contain the R346T and F456L substitutions that you heard about earlier today, shown collectively in the orange curve, that now comprise over 30 distinct sublineages. The most prevalent of these, KP2 in pink, was rising rapidly when it first appeared, but has slowed in recent weeks as other sublineages, like KP3, vie for dominance, both in the U.S. and globally. It's important to note that J1 differs from most of these descendant sublineages, like KP2, by one to five amino acid residues in the spike protein, which is nearly the same range of differences that separated XBB1.5 from other dominant XBB sublineages. In prior years, we have seen that these small genetic differences can, but do not necessarily translate into antigenic differences, as updated vaccines have been effective against descendants of the vaccine-encoded variant, as predicted by virus-neutralizing responses. Humoral immunogenicity data on updated vaccines have, therefore, served as a useful guide in assessing their performance against emerging variants, by gauging the degree of immune escape from vaccine-elicited virus neutralization.

I will now review the clinical immunogenicity of our XBB1.5-adapted vaccine against the homologous and relevant heterologous variants. Here I present the results of a descriptive analysis of XBB1.5 vaccine-elicited neutralizing activity against XBB1.5 and other lineages in a cohort of COVID-19 mRNA vaccine-experienced baseline seropositive adults 18 to 55 years old. These immunogenicity assessments were made one month after vaccination in an authentic virus fluorescent-focused reduction neutralization assay.

We found that the XBB1.5 vaccine elicited robust neutralization not only against the max XBB1.5 lineage in gray bars to the left, but also similarly potent responses against the related but genetically drifted lineage EG51 in blue, highlighted earlier as the dominant one when the vaccine was rolled out last fall. Similarly, BA286, the parental lineage of Jane 1 in purple, was also neutralized.

As I was saying, similarly, BA286, the parental lineage of Jane 1 in purple, was also neutralized well by the XBB1.5 vaccine, despite being phylogenetically distant from the XBB1.5 family, from the XBB family. It's with the emergence of Jane 1 in the green bars to the right, however, that we first observe a reduction in the neutralizing activity consistent with shown earlier and with trends in preclinical models. As preclinical data have closely aligned with clinical responses in prior cycles of variant-adapted vaccine updates, we assess the immunogenicity of a Jane 1-adapted vaccine candidate against Jane 1 and contemporary circulating sublineages of epidemiologic relevance in naive mice.

In the first study of vaccine experienced mice, we found that the Jane 1 vaccine, given as a fifth dose, elicited higher neutralizing activity than the XBB1.5 vaccine against Jane 1 and a broadly representative panel of Jane 1 sublineages. In the study schema shown at the top, mice were first immunized with a vaccine regimen to approximate the antigen exposure of the general

population, first with the primary series of the original vaccine, followed by respective third and fourth doses of bivalent BA45 and monovalent XBB1.5 vaccines. Against this vaccine experience background, mice received a fifth dose of either the XBB1.5 or Jane 1 vaccine and had sera collected one month later for immunogenicity assessments.

Overall, the Jane 1 vaccine elicited neutralizing titers against Jane 1 and related sublineages that were consistently improved over XBB1.5 vaccine responses. Notably, the Jane 1 vaccine response effectively neutralized all Jane 1 sublineages, including KP2-like lineages and their derivatives as well as a next generation of sublineages that have an additional deletion in the spike protein and the KP3 sublineage as well. We quantify the improvement in the Jane 1 vaccine elicited virus neutralization as a function of the geometric mean ratio of the Jane 1 to XBB1.5 vaccine response.

Overall, there is a two to four fold improved response across the panel of Jane 1 sublineages tested, with a trend toward greater fold improvement for the more recently emerging lineages that contain the 346T and 456L mutations as well as the KP3 sublineage. In the second study, we evaluated the immunogenicity of the Jane 1 vaccine as compared to the XBB1.5 vaccine as a primary series in naive mice to mimic the very young pediatric population that has not been exposed to SARS-CoV-2 spike antigens, either by vaccination or infection. As shown in the study scheme at the top, mice received two doses of vaccine at an interval of three weeks. Serum neutralizing responses were assessed in a pseudovirus neutralization assay at four weeks after the last dose. As observed in the vaccine experience model, the Jane 1 vaccine elicited much higher neutralizing responses than the XBB1.5 vaccine against the same broad panel of Jane 1 sublineages, on the order of 10 to 200 fold higher. Here again, the Jane 1 vaccine elicited

similar titers against all Jane 1 sublineages, including KP2 and its derivatives, as well as the KP3 sublineage.

Although the Jane 1 vaccine elicits potent neutralization of a broad panel of salient Jane 1 sublineages, the evolving epidemiologic landscape, particularly with the rise of KP2 and other FLIRT sublineages, prompted us to evaluate the preclinical immunogenicity of a KP2-adapted vaccine candidate as compared to the XBB1.5 and Jane 1 vaccines. In this third study, whose design is depicted at the top, mice were first experienced with two doses of the original vaccine, followed by the bivalent BA45 vaccine, before receiving the XBB1.5, Jane 1, or KP2 vaccine as a fourth dose. Two weeks after the fourth dose, sera were collected for the assessment of neutralization of the same panel of Jane 1 sublineages shown in the prior two studies.

Both the Jane 1 and KP2 vaccines elicited improved responses over the XBB1.5 vaccine. The KP2 vaccine, like the Jane 1 vaccine, elicited similar breadth of neutralizing activity against all Jane 1 sublineages. We compared the magnitude of responses of the Jane 1 and KP2 vaccines relative to the XBB1.5 vaccine, whereas the Jane 1 vaccine elicited two-fold higher responses than the XBB1.5 vaccine, similar to that observed in the prior vaccine experience study.

The KP2 vaccine elicited between three and seven-fold higher responses against this broadly representative panel of Jane 1 sublineages. The summary evidence I presented today supports a vaccine update for the 2024-25 season, whose composition is within the Jane 1 lineage family. This conclusion is based on several lines of evidence. XBB1.5 vaccine had robust effectiveness against XBB lineages that declined against Jane 1. Jane 1 sublineages are dominant with minimal antigenic differences within the family, mirroring observations for XBB lineages relative to the XBB1.5. Jane 1 and KP2 adaptive vaccines confer improved neutralizing responses over XBB1.5 vaccine against a broad panel of emerging variants.

Finally, we are prepared to initiate supply of either Jane 1 vaccine or KP2 vaccine immediately upon approval, and we continue to work to meet public health needs in protecting against COVID-19 as per the committee's recommendation. I thank my many colleagues at Pfizer and BioNTech who contributed to the data shared with you today, and on behalf of them, I thank all our study participant sites, investigators, and partners. Finally, I thank the committee for your time and attention today. My colleagues and I are happy to address any of your questions.

Dr. Monto: Thank you. Dr. Levy.

Dr. Levy: I'd like to thank both the Moderna and Pfizer teams for their very helpful presentation. Recognizing that some of these data had to be generated on short order, because this is a moving target, which is really the point of our hearing today, seems like for some of the analyses, we didn't see actually a statistical comparison stated, so we could see by eye that there are differences in the amount of antibody or the titer, some cases quite evident, but stats were not provided.

So should we presume that for all the statements that were made, that one condition is higher than another, that those are statistically significant? That's question number one. And question number two, it's often practiced in vaccinology studies to demonstrate a horizontal broken line for some sort of correlative protection, recognizing that that's not entirely sorted out for the SARS-CoV-2 vaccines. But relative to the experience of these sponsors, do they believe the titers induced against the most recent variants, JN.1 and its progeny, are hitting a level that they would predict would be protective? Thank you.

Dr. Madjarrod: To your first question regarding the statistical analyses, so these are presented very much in the same way that we present descriptive analyses of clinical study data. However, the assay has a range of about twofold variability. So when we see differences beyond that

twofold difference, we consider that to be a biologically significant difference in responses. With respect to your second question, could you please repeat that so I'm clear on what you're asking?

Dr. Levy: Pfizer, Moderna must have a great deal of internal data comparing performance of vaccines clinically with their ability to induce neutralizing titers across several years now. And based on that information, has Pfizer developed what they believe to be a correlative protection both in the mouse study and in the human neutralizing studies that they believe is a breakpoint above which the immunogenicity should suffice for protection? And if so, how do these results compare to that correlative protection?

Dr. Madjarrod: Currently, there is no correlative protection. I think it's a very well established conundrum in the field that we are still seeking a correlative protection. However, with respect to what justifies a difference in sufficient energetic difference, several cycles of vaccine updates have shown more closely matched vaccines to circulating variants elicit better immunity and protection against COVID-19. Last year, we saw approximately the same fold improvement in responses over the previous iteration of the vaccine, as we are seeing now, and we saw that that translated into improved clinical effectiveness and we expect the same for this year.

Dr. Levy: Thank you.

Dr. Monto: Thank you. Dr. Meyer.

Dr. Meyer: Thank you so much. I wanted to ask you the same question I asked of Moderna related to distribution. It was helpful to see that you are able to initiate supply for either vaccine as soon as possible after approval. What does that mean in terms of volume of doses available at the beginning versus over time? And I think especially in light of the X-ray clips that are coming up this summer for the XBB containing vaccines, particularly in Peds, making sure that we do have that continued supply. Thank you.

Dr. Madjarrod: Yeah, as I mentioned, regardless of whether a Jane 1 or KP2 vaccine is selected, we are committed to having sufficient doses available and shipped immediately upon approval. With respect to some of the details of the supply throughout the season and to the question about the pediatric, I'll ask my colleague, Dr. Bill Faulstich, to come up and address that question.

Dr. Faulstich: Hi, good morning, Bill Faulstich. I'm the Vice President of Global Supply Chain here at Pfizer. So first of all, with regard to pediatric supply, we will have ample supply regardless of whether it's Jane 1 or KP2, just based on the volume that we're able to generate relative to the demand we have. And then just to reiterate what's already been said, regardless of whether it's Jane 1 or KP2, we've evaluated the expected demand we'll have throughout the vaccine season. And we expect that we can supply, whether it's Jane 1 or KP2, that we can supply the quantities needed. So we expect sufficient supply.

Dr. Monto: Thank you very much. Dr. Gans, final question.

Dr. Gans: Thank you so much. This really is going to apply to the three manufacturers. So there was one sentence that the safety of the vaccines that have been in use for some time were, there was no increase in safety events for the Moderna. I didn't hear anything from Pfizer on the safety of the vaccines that have been in use. I know surveillance is robust and vigorous, and we would love to hear some information on that. I know it wasn't part of your presentations, but we do have follow-up ability to hear from you later this afternoon. So it would be great if we could have updates. Yeah, but I'm asking for them to-

Dr. Monto: Later in the afternoon, so we can get it from all three.

Dr. Gans: Yeah, exactly. That's what I request.

Dr. Modjarrad: Can I just state that we have not seen any differences in safety signals, and the safety profile is the same for the most recent adapted vaccines as they were for previous iterations of the vaccine.

Dr. Gans: Yeah, but we'd like to see it over time. Thanks.

**Novavax Presentation: Novavax Data in Support of 2024-2025 Vaccine Update**

Dr. Monto: Okay, thank you. Moving on to Novavax. We are going to hear from Dr. Walker about Novavax's position in terms of the strain selection.

Dr. Walker: Good morning. I'm Robert Walker, Chief Medical Officer at Novavax. And I'd like to first thank the committee and the FDA for the opportunity to present our data.

Today, I'll briefly discuss relevant strain surveillance data, followed by a presentation of immunogenicity results from our recent XBB1.5 clinical trial, and I'll conclude with non-clinical immunogenicity data for our candidate JN.1 vaccine. In sum, we believe these data support a JN.1 lineage COVID-19 vaccine update for the 2024-25 season. Our vaccine platform combines two components.

First, recombinant protein particles comprised of full-length spike trimers, shown here in red, expressed in a baculovirus insect cell production system and configured in a rosette pattern around a core of polysorbate 80, shown here in blue. And second, matrix M, a saponin-based adjuvant that has been shown to increase the magnitude and breadth of the immune response. These two components are co-formulated as a liquid suspension, and the final product is a refrigerator-stable injectable vaccine, which this year we expect to have available in the U.S. as a prefilled syringe.

I will now turn to some recent data on U.S. surveillance. This table, which you've seen previously today, lists in descending order the SARS-CoV-2 strains that are currently circulating in the U.S. at rates of 1% or more. All of the currently circulating variants, and there are 15

different ones listed on this slide, are descendants of the parental JN.1 strain and acquired their additional mutations along multiple different pathways, all of which radiate from JN.1. While some variants containing the so-called FLIRT mutations, such as KP2 in blue-gray and KP11 in yellow-green, have been increasing in frequency over the past six to eight weeks and currently account for over 40% of certain sequenced isolates, there are other non-FLIRT subvariants that have also been steadily increasing in frequency, such as KP3 in the plum color. There are also other JN.1 lineage subvariants with different mutations and combinations of mutations that have been persisting over many weeks, as is evident in this figure, as the multiple colorful bands making up the lower third or so of the frequency bars. So, while the current focus is on the FLIRT subvariants, it's far from certain that the variants that will predominate this fall will emerge from the KP2 cluster, and other variants such as KP3 may predominate.

The JN.1 lineage subvariants can be grouped according to the mutations they've acquired in addition to those of the parental JN.1 strain. Examples of these groupings are shown in this slide and include the FLRT, FLIRT, FLIRTE, and FL plus QE subvariant groups. I'll be referring back to these mutations of interest throughout the presentation. An important tool that's been used to help assess the degree of antigenic relatedness between strains relies on serology and antigenic cartography to map the three-dimensional distance between strains. In these maps, each square in the grid equals one antigenic unit or a two-fold difference in antibody titers. Shown in this slide are antigenic distances measured in our hands from experiments in vaccinated mice between prototype and VA5, VA5 and XBB1-5, and between XBB1-5 and JN.1.

In each case, the antigenic distance exceeds four antigenic units, with four antigenic units being the equivalent of a 16-fold difference in neutralizing antibody titers. As a point of reference for influenza strains, a cutoff of less than or equal to two antigenic units is often used

to infer antigenic similarity. Shown here are data from a preprint you've seen earlier today and presented at a recent WHO meeting that displays the antigenic distance between JN.1 and its recently emerged subvariants based on neutralizing antibody titers in vaccinated mice.

These data show the mostly overlapping JN.1 lineage subvariants in the blue box with a blown-up image of this area of interest on the right. Most of the variants cluster together, and even KP3 is within approximately one antigenic unit of JN.1 and the other clustered variants. From these data, we conclude that JN.1, KP2, and KP3 are all antigenically similar.

In the next few slides, I'll present our own data that supports selection of JN.1 for the vaccine update for the 2024-2025 season. These data include clinical study results in a previously vaccinated and infected population showing antigenic similarity of currently circulating JN.1 lineage subvariants as evidenced by the minimal differences in neutralizing antibody responses for these subvariants after receipt of the Novavax XBB15 vaccine. I will also show data from non-clinical studies demonstrating that our JN.1 vaccine generates broad neutralizing responses for JN.1 lineage subvariants containing the FL, RT, FLIRT, and FLIRTI mutations, and for KP3 containing the FL and QE mutations. And I'll present non-clinical data showing that our JN.1 vaccine, like our previous ancestral and XBB15 vaccines, induces a polyfunctional Th1-biased T-cell response that recognizes conserved T-cell epitopes across JN.1 lineage subvariants. I'll begin with data from our XBB15 clinical trial. This study used an open-label, single-arm design. It was conducted in the U.S. and enrolled adults who had previously received three or more doses of mRNA vaccines, with the last dose being at least 90 days prior to enrollment. In the study, participants received a single dose of our XBB15 vaccine. While the primary measures were safety, reactogenicity, and serologic responses to the XBB15 vaccine stream, for the purposes of

today's meeting, I will present cross-reactive neutralizing responses to the forward-drift JN.1 lineage subvariants we've been discussing.

Shown here are results pre- and post-vaccination with XBB15 in a random subset of 59 of the 330 study participants for JN.1 and for a number of JN.1 lineage subvariants. For the JN.1 stream, the baseline titer was 45, and the day 28 titer increased 5.6-fold to 247, indicating robust cross-neutralizing activity. For the other JN.1 lineage subvariants tested, including those containing the FL, RT, FLIRT, and FLIRT mutations, the fold rise ranged from 5 to 7, with geometric mean titers generally comparable across variants.

These data indicate that in previously vaccinated and infected populations, which defines the majority of the U.S. adult population at present, we observed minimal differences in the levels of neutralizing antibody responses for the JN.1 lineage subvariants, even after vaccination with a heterologous XBB15 strain. These minimal differences among the subvariants closely align with the degree of antigenic relatedness we saw in the figure presented by WHO in mice. I will now discuss recent non-clinical data evaluating our updated JN.1 vaccine. In this experiment, a group of five rhesus macaques were primed and boosted with a total of three doses of XBB15 vaccine before receiving an additional dose of JN.1 vaccine after 11 months. Neutralizing titers are shown at 14 days following the JN.1 dose, and antigenic distance relative to JN.1 is shown in the table to the right for the JN.1 lineage subvariants. Following receipt of the JN.1 vaccine, broad neutralizing antibody responses were seen for the homologous JN.1 strain in dark blue to the extreme left, and for all of the subvariants tested, including those with the FLIRT mutations, and for the KP3 subvariant.

The geometric mean fold rises for the subvariants range from 13 to 32, consistent with this broad cross-neutralization. As can be seen in the table to the right, the antigenic distance

between JN.1 and each of the variants, including KP2 and KP3, were all less than 1.5 and often less than 1, indicating antigenic similarity. This slide shows similar results in mice primed with two doses of XBB15 vaccine before receiving an additional dose of JN.1 vaccine at two months.

Here again, we see broad neutralizing antibody responses to the homologous JN.1 strain in dark blue to the left, and to all of the subvariants tested, including those with the FLIRT mutations, and to the KP3 subvariant. The geometric mean fold rises ranged from 18 to 59, again, consistent with this broad cross-neutralization. And as can be seen in the table to the right, the antigenic distances between JN.1 and each of the subvariants, including KP2 and KP3, were at most 1.11 antigenic units, indicating antigenic similarity.

We also have evaluated cell-mediated immune responses in the mice that received a priming series with XBB15 and an additional JN.1 vaccine dose at two months. Just as we have consistently demonstrated for our ancestral strain vaccine and our XBB15 vaccine, the JN.1 vaccine also induced Th1-biased CD4 positive T cell responses to conserved T cell epitopes, as measured here by triple cytokine positive staining of CD4 cells stimulated with spike protein from a range of omicron variants, including KP2. In closing, we believe that the data I've reviewed with you today support a JN.1 vaccine update for the coming season.

Our JN.1 vaccine generates broad neutralizing responses for JN.1 lineage subvariants when administered to XBB15 non-human primates and mice. These cross-neutralizing responses were seen for subvariants with the FL, RT, FLIRT, FLIRTE, and FL plus QE mutations. Selecting a vaccine strain that is antigenically similar to a broad range of circulating strains and not necessarily the currently dominating strain may be an approach to de-risk the selection process. Our vaccine also induces a conserved polyfunctional Th1-biased T cell response against JN.1 lineage subvariant viruses. Our data support a JN.1 lineage vaccine update for the 2024-2025

season aligned with WHO and EMA recommendations. A recommendation from this committee for a JN.1 vaccine will enable a protein-based vaccine option to be available to the U.S. population this fall.

If the recommendation precludes use of a JN.1 vaccine, then a protein-based option will not be available in the U.S. for the fall vaccination effort. Finally, commercial manufacturing is ongoing and initial shipments of our JN.1 vaccine are on track to be in U.S. warehouses in August. And with that, I'll conclude and thank you for your attention.

Dr. Monto: Thank you very much, Dr. Gans.

Dr. Gans: Thank you so much. Thanks for the T cell data, by the way. A quick question. What was the time interval from the prime boost to the pre-sampling that you have just before the boost? So when did they get there? What time elapsed between the priming to give us the serologic titers that you see in your pre-boost vaccines?

Dr. Walker: Dr. Ganz, you're talking about the clinical data with the XBD vaccine?

Dr. Gans: Yeah, the non-clinical in the macaques that were given priming doses and then a boost, and you have the pre/post-boost serologic data. And I'm wondering what was the time interval between their priming doses and that pre-vaccine dose, pre-boost? If you could go to your slide, I could show you.

Dr. Walker: I'm not understanding the question.

Dr. Gans: So they got primed with two doses of something, XXB, and some of the models and other. What was the time from the last priming dose and that pre-sample?

Dr. Walker: So I understand your question, thank you. So they received two doses of the XBB1.5 initially one month apart, a third dose of XBB1.5 at month six, and a JN.1 dose at month 11.

Dr. Gans: So there was, five months had elapsed and then you got those titers.

Dr. Walker: Correct.

Dr. Gans: Thank you.

Dr. Monto: Thank you, Dr. Perlman.

Dr. Perlman: Yeah, just a quick question. So in previous Novavax trials, the CD8 T cell response wasn't induced initially, but was with repeated boosting. Are you seeing a CD8 T cell response here?

Dr. Walker: Thanks for that question. We have not evaluated CD8 T cell responses in this particular study. As has been published previously, we do see CD8 cell responses in a small subgroup of individuals with their initial priming series, but it's not a common phenomenon.

Dr. Perlman: Thank you.

Dr. Monto: Dr. Meissner, last question.

Dr. Meissner: Thank you, Dr. Monto, and thank you, Dr. Walker for that presentation. Very simple question. I want to make sure I understood that the only vaccine that Novavax will make available is the JN.1.

Dr. Walker: So we are currently manufacturing JN.1 vaccine. That's correct. So in order to have a protein vaccine ready to go September 1, we're prepared to provide the JN.1 vaccine. We think, based on the data I've shown you today, that the JN.1 vaccine is appropriate and has good cross-neutralizing activity against all the subvariants that are currently circulating. So that is the plan, yes.

Dr. Meissner: Thank you.

## FDA Presentation: FDA Considerations and Recommendation for Changes to COVID-19 Vaccine Formula Composition

Dr. Monto: Thank you. I think that's very clear. Okay, we're going back to Dr. Jerry Weir, FDA, who will give us the considerations and recommendations for changes to COVID-19 vaccine formulation composition. Dr. Weir.

Dr. Weir: Thanks. I know we're a little short on time. I'll try to be as fast as I can. You've heard a lot of information today already, and I'm going to repeat some of it. I'll try to hone in on the points that I think are worth repeating. The first few slides, I started with some background.

I know most of the committee has been around for several years, but not everyone. But I wanted to just give you a reminder of the type of questions we asked ourselves the last few years and what the deliberations were. So I'll try to go over this pretty fast.

We've met four times to talk about COVID vaccine updates. The original April 6 meeting, as well as a follow-up on January 6, 2023, were to discuss the framework itself. And I think we came to an agreement about several things here that there should be a periodic assessment by the FDA and the VRBPAC. It should be a data-driven thing. And at the time, we concluded that a late spring, early summer target for review and recommendation was reasonable, but we all acknowledged that we would modify that as needed. Two different times, last June and the June before in 2022, we actually discussed specific recommendations for updating the vaccine. And I'm going to show those in the next few slides just to remind everybody what we did. Okay, so this is the variant situation in June 2022.

As Dr. Thornburg has mentioned several times, these dendograms on the left are not phylogenetic trees. They just show relationships. But this was what we were seeing in 2022, in June 2022. The Omicron variant had been replaced starting the previous December, but by June,

it had completely replaced all the previous SARS-CoV-2 viruses. And at that time, manufacturers had produced and evaluated a BA1 vaccine in clinical trials, and they were prepared to supply a BA1-containing vaccine for 2022-23. But when we met in June, BA1 was no longer in circulation, and it actually was extremely antigenically distant, distinct from BA2-derived viruses. And so the discussion hinged on the selection of the particular sublinage variants versus BA1 versus BA45. Next slide. Okay, so to summarize, the committee met on June 28, 2022, to consider whether a change to the vaccine composition was needed. And at that time, the committee discussed evidence supporting a monovalent Omicron or a bivalent vaccine, which would have been the prototype plus an Omicron component. And they also discussed the selection of specific Omicron sublinages, for example, BA1 versus a BA45. The committee voted to recommend inclusion of the SARS-CoV-2 Omicron component for booster vaccines in the United States, and there was a general preference for a bivalent vaccine containing both the ancestral and the Omicron strain.

Following that meeting on June 30, FDA notified vaccine manufacturers of our recommendation to develop a bivalent vaccine. This was the prototype or ancestral plus an Omicron BA45. The first bivalent vaccines from Moderna and Pfizer-BioNTech were authorized for use in individuals 18 and of age and older and 12 years of age and older, respectively, on August 31, 2022. A year later, in June 2023, this was the variant situation.

At this point in time, XBB lineage viruses had replaced previous BA5-derived SARS-CoV-2 viruses, and that's shown in the top left and also on the right. The XBB viruses were recombinant viruses from two earlier BA2-derived viruses. The VRBPAC discussion concerns selection of XBB lineage viruses, for example, XBB1.5, 1.16, 2.3. And the data that we had at the time last June was that the XBB1.16 and the XBB2.3 differ from XBB1.5 by one amino acid

in the RBD, and there was generally overall evidence that suggests that there was a lot of similar antigenic similarity among all of the lineage viruses that we were in consideration. The next slide shows a summary of that VRBPAC meeting.

We met on June 15, once again to consider whether a change was warranted. The committee discussed the evidence supporting an updated XBB lineage COVID-19 vaccine as well as the selection of specific XBB lineage, and we talked about these various strains that I just mentioned. In the end, the committee voted to recommend an update of the vaccine composition to a monovalent XBB lineage for the United States, and there was a consensus that based on the data presented as well as other practical considerations, the XBB1.5 sub-lineage should be selected for the 2023-2024 COVID-19 vaccine.

Following that meeting, the next day on June 16, FDA notified vaccine manufacturers of our recommendation to develop a monovalent XBB1.5 vaccine for age appropriate use in potentially eligible populations. These updated XBB1.5 monovalent mRNA vaccines from Moderna and Pfizer BioNTech were approved and authorized for use on September 11, 2023, and an updated XBB1.5 adjuvanted COVID-19 vaccine for Novavax was authorized for use on October 3. So that's the last couple of years. Now this year, we're considering changing and modifying the COVID-19 strain composition again.

So I want to spend two quick slides going over some of the major considerations that we need to consider this year as well as every year when we go through this process. The key questions to be addressed by the agency and the VRBPAC in considering whether to modify the COVID-19 vaccine composition include the following. Have currently circulating SARS-CoV-2 virus variants become or are they expected to become dominant and displace earlier virus strains? Are currently circulating SARS-CoV-2 virus variants antigenically distinct from current

vaccines? Is there any evidence that current vaccines are less effective against new circulating virus variants than against previous strains of virus? And finally, is there evidence that a candidate vaccine with an updated composition will be more effective against the new circulating virus variants and provide an improved clinical benefit? Along with these considerations, there are a couple of assumptions that we need to keep in mind.

Okay, so since broad spectrum variant proof vaccines do not yet exist, current spike-based vaccines will continue to need periodic updating to maintain effectiveness as SARS-CoV-2 continues to evolve. Since virus neutralization is important for protection, especially for these spike-based vaccines, clinical and non-clinical virus neutralization data are powerful tools that can be used to inform the vaccine composition process.

For vaccines with prior demonstration of efficacy, which is the ones we're talking about at this meeting, the data package needed for regulatory review will include comprehensive chemistry manufacturing and control data to ensure product quality, in addition to non-clinical data, animal data, that supports effectiveness of the updated vaccine formulation. We also will still require clinical data post-authorization of approval, even for these vaccines with prior demonstrated efficacy, so that we can have an ongoing evaluation of the vaccine composition process. Regardless of the manufacturing technology, the timelines for production and regulatory approval of an updated vaccine are constraining, and they necessitate that manufacturing, some manufacturing activities be performed at risk for any sort of timely vaccine rollout.

Now, as I said, we've covered a lot of this in the previous presentations, so I'm going to touch on some of the various considerations that you've already heard I want to highlight. The next slide, I want to talk about current effectiveness of authorized COVID-19 vaccines. You heard a lot of information from the CDC, as well as from the WHO. Overall, observational

effectiveness data that we have currently has indicated that the effectiveness has indicated the effectiveness of the 2023 XBB 1.5 vaccines. The data also strongly supports that our updating of the composition this last year from the 2022 bivalent vaccine did offer benefit and protection. Nevertheless, vaccine effectiveness appears to decrease as time since vaccination increases, and as new SARS-CoV-2 variants emerge.

I wanted to show one quick piece of data from a recent New England Journal of Medicine publication. This was interesting for a couple of reasons, and this had to do with data from Nebraska State Immunization Information System, where they actually measured effectiveness against infection as well as hospitalization of the XBB 1.5 vaccines. And what you see is that when you look at the top panel or the bottom, that effectiveness of the vaccines and the XBB 1.5 vaccines peaked at about four weeks and then slowly declined. This is similar to what we've seen for several years now.

What they also did was to separate these effectiveness for vaccination and hospitalization as per time of vaccination, depending on the current variant circulating. That's what you see on the right. If you look at the same curves against times when XBB 1.5 and its derivatives were present versus JN.1, you see a same pattern of curve, but you see that the effectiveness starts out higher when there's a better match against the XBB. Basically, what that's saying is strongly suggesting that match does matter somewhat.

I want to touch on something you've heard many times already today, and that's the current surveillance and genomic analysis. This is the same dendrogram that Dr. Thornburg presented, and I only put it up there to highlight a couple of things.

One is she points out this is a relationship map, but the other thing to point out is from left to right, it's not temporal. In other words, the times are not linear from left to right. I've put in

some designations for when these different variants were active, but the point to make from this is that XBB lineage viruses were almost completely displaced by BA286 and JN.1 lineage viruses by early 2024. The other point that's already been made is that these BA286 JN.1 lineage viruses are not derived directly from XBB lineage viruses, and they're antigenically distinct. As you've already heard also several times, JN.1 has continued to evolve with some concerning mutations in the spike protein.

You've also seen this several times now. This is the now cast variant proportions. I won't go over the actual numbers except to point out that I put on the right the virus variants, everything above about 3%, and whether they're increasing in proportion or decreasing.

If you look at the ones that are increasing proportions, such as KP2, KP3, even KS1, you go to the next slide. I've correlated these with the common amino acid changes in the spike protein relative to JN.1. On the left, you see the lineages KP2, 3, KP1.1, 16.1, and KS1.

These are all increasing in proportion, and they all have some common mutations relative to JN.1. These are the ones you've heard about several times, 346 and 456. The interesting thing here is, and again, I think this has already been mentioned, is the 346T was in the XBB vaccine and in all of the XBB lineage viruses.

When JN.1 emerged, it had an R just like the earlier BA2, but now it's being strongly selected for the T at that position. The 456 position was strongly selected as XBB lineage viruses evolved. When XBB1.5 emerged, it actually had the F at that position, but the L was replaced as those viruses emerged into EG5.1 and HB1.

Okay, so again, as already mentioned, the reason these are somewhat concerning is because these are examples of convergent evolution. In other words, they've appeared before,

and they presumably confer an advantage to the virus in terms of fitness or escape from immunity.

All right, now I want to touch on post-vaccination human serology studies. Again, you've heard a lot of information from various sources today, but to summarize, post-vaccination human serology studies are used to evaluate antibody responses generated by current vaccines. In other words, XBB1.5 vaccines against more recently circulating virus variants such as JN.1. Post-vaccination sero are available only from recipients of current XBB1.5 vaccines. The neutralization titers that are measured against new variants, such as the JN.1, KP2, other viruses, can reveal significant immune evasion against these viruses compared to the vaccine, but they only indirectly suggest similarities or differences among those variants themselves. Now, you've heard data presented at this VRBPAC by the manufacturers of the approved, authorized vaccines, as well as from other studies that indicate that recent virus variants, particularly JN.1 lineage viruses, are more immune evasive to antibodies elicited by prior XBB1.5 vaccination.

And I have one slide, the next slide, showing one other study that is similar to the ones you've heard about. This was a study done at the Uniformed Services University, and the PI was Edward Mitra, but the neutralization data, the pseudovirus neutralization data was done by Carol Weiss's lab here at CBER. But essentially, you see what you've already shown, and this is that in vaccinees, whether they've been previously infected or not, boosting with XBB1.5 increases titers against XBB1.5, but there is a significant drop-off against JN, when analyzed against JN.1.

The other interesting thing that they did was to look at the, in the pseudovirus neutralization assay, the selected mutations that we just talked about at 346 and 456, and here you see when you do neutralization titers against these pseudoviruses in the assay, you see a further drop against viruses that have those mutations. Next slide. Okay, non-clinical

immunogenicity studies with new candidate vaccines. This is what you've heard from all three manufacturers. Non-clinical immunogenicity studies are used to evaluate immune responses generated by new candidate vaccines, those expressing or containing updated spike components against antigenically distinct circulating virus variants. This non-clinical immunogenicity data, which is animal data, and it's almost exclusively neutralizing antibody, can provide an indication of how well the antibodies to the spike of one strain will cross-neutralize other variant strains of SARS-CoV-2, and that thus helps us inform our strain selection in combination with other data.

All of these studies are dependent on COVID-19 vaccine manufacturers producing candidate vaccines at risk and conducting the studies to generate the data for evaluation. I will remind you, though, that the study designs are very heterogeneous and they do not fully recapitulate a human exposure. The data presented, though, by all of these manufacturers of authorized and approved vaccines indicates, though, that candidate vaccines with an updated JN.1 lineage formula, monobated formulation, elicit stronger neutralizing antibody responses against JN.1 and JN.1-descendant viruses than against current XBB, then new current XBB1.5 vaccines, but the levels of the neutralizing titer do vary depending on the variant.

Next slide. Okay, the last couple of slides, the last few slides, I want to turn to something that we haven't discussed a lot today, and that's post-infection human serology studies. So, in the previous few slides, I mentioned post-vaccination human serology. Those studies, as I pointed out, are limited to sera from recipients of current vaccines, but we also have now several serology studies using sera from individuals infected with a more recent JN.1 virus variant. The data that I'm going to show you in the next few slides indicates that JN.1 infection elicits higher JN.1-specific neutralizing antibody titers than an XBB virus infection, but JN.1 infection also elicits neutralizing antibody titer against JN.1 lineage viruses, including those with the

concerning spike mutation, but the titers against the more recent circulating strains of JN.1 and lineage viruses appear reduced relative to JN.1. The caveats are kind of the same caveats you have for all the data we hear at these meetings.

There are limited numbers of sera for analysis. There are different exposure histories of the subjects, and of course, with the several studies I'm going to show you, all of them use different assays. So, study one is in the next slide. Okay, this was a study that had sera from 12 individuals who had been infected with JN.1. Different vaccination exposure histories, but what you see on the left graph, the last two panels, the titers against JN.1 versus KP2, and here you see that there is a significant, in their hands, a significant difference in the titers of KP2 compared to JN.1. Study two is shown on the next slide, also a bioarchive. Actually, this study was presented by David Wentworth in his presentation, and if you remember, it was a complicated slide. I plucked out three of the panels that had to do with the cohorts that had JN.1 infection, and I've circled the parts that I wanted to highlight. Okay, so these were three different cohorts, including actually naive humans that only had JN.1 infection, but also some that had sequential infections, as well as some that had been vaccinated with sequential infection, and in all cases, you see titers against JN.1 were improved relative to the panels.

I'm not showing you against XPV1 infection, but also you see lower titers against variants that were analyzed that had either the 346T or the 456L mutation introduced into the assay. Study three, next slide, also a recent publication in bioarchives. This was one with seven sera samples from BA2 JN.1 infected subjects.

Again, in this one, they analyzed the neutralizing titers against these JN.1 infected individuals against JN.1, and then against KP2, as well as in their hands, what they're calling SLIP is the one that has the F456L mutation, and the FLIRT, which has the 456 as well as the

346R mutation. Again, you see a pattern of decreased antibody titer with the introduction of those particular mutations. And finally, study four, which I just, next slide, which just came out this past week in bioarchives, these were 10 sera samples from a JN.1 infected cohort.

Again, if you look at, I think it's one through three bars over, you see the titers of this 10 sera tested against JN.1, and these investigators tested, again, also in a pseudotype neutralization assay against JN.1 with the introduced mutations at 346, 456, and also 557. They concluded from their work that F456L is a major dryer of antibody evasion. Okay, so that's a summary of what we have available for post-infection studies.I'll stop there and summarize.

Okay, so the next two slides are a summary. By several measures, including increased escape from antibody neutralization and waning protection, COVID-19 vaccines appear less effective against currently circulating variants such as JN.1 lineage viruses than against previous strains of virus. You've already heard that manufacturers of authorized approved COVID-19 vaccines have been evaluating updated candidate vaccines at risk, and they are prepared to provide an updated vaccine formula for 2024-25. The manufacturing timelines may be impacted by the final choice of the vaccine antigen.

The next slide, a few more summary bullets. Non-clinical data from three different vaccine manufacturers indicate that updated monovalent JN.1 lineage formulations elicit stronger neutralizing antibody responses against JN.1-descendant lineage viruses than current monovalent XBB1.5 vaccine. Virology data from JN.1-infected individuals also indicates improved neutralizing antibody responses against JN.1 descendant lineage viruses compared to serum from XBB-infected individuals, but the neutralizing antibody responses appear to be reduced by recent amino acid mutations in many of these JN.1 lineage viruses.

The totality of the available evidence indicates that a monovalent JN.1 lineage vaccine is warranted for COVID-19 vaccines of the 2024-2025 formula to be used in the U.S. to more closely match circulating SARS-CoV-2 viruses. The diversity of the JN.1 lineage viruses complicates somewhat the specific strain selection decision. The last slide is a couple of observations, next slide, a couple of observations about the future directions of this process.

I think we've all resigned ourselves to the fact that updating the SARS-CoV-2 strain composition for vaccines is going to be a continuous process, but I think we've also, it's becoming clear that the ideal timing for a vaccine composition decision remains elusive. The virus continues to evolve without a well-defined seasonality, vaccine production timelines differ depending on the manufacturing technology, and there is still uncertainty regarding the optimal timing for vaccine administration. In other words, trade-offs are inevitable in the timing of the vaccine composition decision.

And finally, I want to mention that this process, there are still many challenges that remain, and I think Dr. Wentworth mentioned some of these too, but I'll highlight them again. At the time we make these decisions, there is a limited amount of critical, non-clinical, and clinical data available at the time we must make the recommendation. We still poorly understand how the differences in neutralization titer relate to clinical outcomes. The current non-clinical models, the animal models that we're using imperfectly reflect the human populations receiving the vaccine, and human post-vaccination and post-infection serology panels are simply not available for distinct populations, such as pediatric, adult, elderly, who may respond differently to vaccination or infection. I'll stop there. We can flash up the questions again, but you saw them in my earlier introduction. This will be the voting question.

Dr. Monto: Dr. Weir, yeah, why don't, we're facing a hard stop because of the oral public hearing. What I'm going to propose is that we start, we go to the oral, the public hearing, and that you start the discussion with the questions at that point, at two o'clock eastern.

Dr. Weir: Yeah, that sounds good. I mean, we'll just flash these up and start.

Dr. Monto: Yeah, why don't you flash them up right now so people can think about them, and then we will come back to maybe your summary slide and go into this for the robust discussion we're going to have it two o'clock. No questions now.

Dr. Weir: This is the voting question. You saw this earlier. The next slide shows the discussion topic. Okay, so that's what we will vote on and discuss later this afternoon. I'll stop there. Thanks.

Dr. Monto: Okay, thank you, and we're going to go straight to the lunch break, and then the, we will have the oral public hearing, and we'll come back and start out with some of the hands that are currently raised, and go into the discussion of the, first the voting question, and then the hard discussion about what variant in the vaccine. So, break until one o'clock for oral public hearing.

**Open Public Hearing**

Dr. Monto: Meeting. We are beginning the Open Public Hearing. 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 of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial response relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of expenses in connection with your participation in this meeting. Likewise, the FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such

financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. Over to you, Kathleen.

Ms. Hayes: Thank you, Dr. Monto. And before I begin calling the registered open public hearing speakers, I would just 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 your views and comments. FDA encourages participation from all public stakeholders in its decision-making process. 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 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 reflect the viewpoints of the individual speakers or their organizations and are not meant to indicate Agency agreement with the statements made. And with that guidance, we can begin. So, I just want to note that each speaker will have four minutes to make your remarks. And we will begin with our first speaker, Paul Hennessey.

Mr. Hennessey: Hi, my name is Paul Hennessey. No conflicts, no associations to report. COVID vaccines need to be available by August. All three vaccines should be approved simultaneously and rolled out before the school year. We're already in another surge, so waiting until September will result in more needless infections. The new COVID vaccine should target JN.1 as per WHO recommendations. All JN.1 vaccines show promise against sub-variants like KP2 and three as well, but all these variants are especially transmissible. So this year, two doses two months apart should be the series. This should be applied to both mRNA and protein-based vaccines. Two doses will provide the best protection from not just JN.1, but also KP2 and three. Novavax has a

broader range of protection for multiple variants than mRNA vaccines, so their current JN.1 vaccine will also protect against FLiRT variants. However, a second dose will give a boost that makes for not directly targeting KP2 and three and overcome imprinting. The fall strategy by the FDA should provide two doses of either Moderna or Novavax. This will provide the best possible protection going into the fall. Recommending companies retailor the vaccine this late in the year will result in significant delays for all vaccines and no protein-based alternative for those of us who need one, which is unacceptable and dangerous.

Novavax must be approved. Under no circumstance should the only option be mRNA, especially since Novavax's JN.1 vaccine provides substantial protection against KP2 and three. All vaccines should be approved simultaneously. Last year, Novavax approval was delayed, leaving a lot of people, including myself, waiting weeks for their preferred vaccine. It added unnecessary risk. I think I speak for a large number of us who are worried that Novavax will once again be restricted. FDA must also approve the pediatric Novavax. We've waited far too long for the safe and effective vaccine to be available for children.

Furthermore, COVID vaccines should be updated and approved for everyone every six months. COVID does not peak in the winter only. Cases are surging right now. Variants are changing so rapidly that vaccines should be updated and recommended for everyone every six months. You said it yourself; waiting is an issue. People are turning to blaming the vaccine as health issues from repeat COVID infections become obvious. Twice per year updates for everyone, not just immunocompromised, should be the norm. When the new vaccines are ready, it's important to stress a layered approach. FDA's messaging must encourage the public to take multiple precautions, like masking and improving air quality, on top of the vaccine for best possible protection. An over-reliance in the vaccine-only approach has also contributed to public

mistrust and mass reinfection. We need to be realistic about the vaccine's shortcomings. FDA should also pressure the CDC to reinstate and expand the bridge access program for free vaccines and return the COVID isolation guidelines to 10 days.

Looking ahead, we need more urgent funding and work groups for expedited intranasal vaccines, specifically prioritizing nasal vaccines for Covovax and Novavax. These are protein-based, non-annotated (phonetic) vaccines which are promising. More funding is also needed for COVID and long COVID studies and treatments, including repurposed and novel antivirals, antiviral infusion, monoclonal antibodies, and immunotherapies. I'd also like to voice my concern with vaccine companies' attempt to create a COVID-flu combo vaccine. These illnesses are too different and combining them will only water them down in the same way the bivalent COVID vaccine was watered down. I want protection, not convenience. FDA should, however, study the use of Matrix-M adjuvant in other vaccines. It improved the malaria vaccine, so there should be more studies to see if it can improve vaccines for flu, RSV, MMR, and H5N1. Improving existing vaccines is important because immune systems are damaged from repeat COVID infection.

To recap, the most important thing you could do right now is recommend two doses for a JN.1 vaccine two months apart for the best possible protection, then allow vaccination every six months for updated variants targeted. Please expedite and roll out vaccines from all three companies in August. Thank you.

Ms. Hayes: Thank you. Our next speaker is Antonio Barrero.

Mr. Barrero: Hello, everyone. This is Antonio Barrero from HIPRA scientific project manager. On behalf of HIPRA, I'd like to thank the organizing committee for the possibility to present today.

HIPRA is a biotech company located in Spain with more than 50 years of experience in the development of innovative vaccines. In 2020, we started the development of a COVID-19 vaccine known as PHH1B. It was successfully evaluated by EMA and the UK Regulatory Agency and approved for commercialization in Europe. It is known by the commercial name of Bimervax. Also, it is the only COVID-19 vaccine pre-qualified by WHO. We can proudly say that HIPRA is one of the very few companies in the world to continuously monitor the SARS-CoV-2 evolution and making efforts to adapt the vaccine to currently circulating variants. Next slide, please. PHH1B is a recombinant protein-based RBD heterodimer combining the beta and alpha variants. RBD is well-recognized to be a potent immunogen. It is adjuvanted with an oil and water emulsion that comprises well-known components. The vaccine has demonstrated to be efficacious and safe and is indicated as a booster dose in people over 16 years old and after receiving a primary boost vaccination with mRNA, and also after the same PHH1B.

Of note, this antigen allows to design both bivalent or monovalent antigens, offering more possibilities to provide vaccines targeting different variants. Following official recommendations, HIPRA started the monovalent adaptation to the HPV1 lineage, by designing an HPV116 RBD homodimer. For this first vaccine adaptation, a clinical trial had to be conducted to demonstrate adaptability. This first adapted vaccine is in the final stages of evaluation by EMA. Also, we are already finishing the development of a newly adapted vaccine based on a JN.1 homodimer, and we expect it to be available for the next full vaccination campaigns in Europe. To be clear, this vaccine is not available yet in the U.S., although we look forward to bringing this vaccine in the future and contribute to the vaccination programs. Next slide. Here you can see clinical data of our first adapted vaccine to HPV, known as PHH1B81. In this trial, the common HPV1.5 mRNA vaccine was used as a comparator. We obtained superior

neutralizing antibody responses, both against HPV116 and HPV15, and also in total antibody titers. Next slide. Interestingly, higher neutralizing antibody titers measured by live virus neutralization assays were observed against both PHH286 and JN.1 variants, confirming the cross-reactivity and good resistance against new and divergent variants. This is a powerful feature of this vaccine design that was previously demonstrated for the parent vaccine. Next slide.

It is important to note as well that this vaccine elicits a significant cellular immune response, not only against HPV-derived variants, but also against JN.1. Specifically, stimulation of PBM6 demonstrated a significant increase in interferon gamma expression lymphocytes, after the booster dose with the HPV adapted vaccine. Next slide, please. HIPRA is committed to following the adaptation recommendations. For this reason, in the beginning of 2024, a JN.1 adaptation known as PHH1B101 was initiated at risk. Preclinical data obtained in mice with this new vaccine, for either two-dose prime vaccination or booster assays, showed that the JN.1 vaccine generated good neutralization titers against JN.1. As expected, bigger differences are obtained in the prime booster assay, where a specific response against JN.1 is expected for native animals. In the booster assay, the JN.1 adapted vaccine showed also higher titers against JN.1, although the HP- adapted vaccine was able to induce as well a significant neutralizing response against this distant variant. Next slide, please. Finally, the cross-neutralization is being assessed also against JN.1 sub-lineages. Very good neutralization titers are observed against JN.1 descendants that are currently circulating, including KP2. These results are consistent with the cross-neutralization capacity previously demonstrated for this particular vaccine and confirm that our JN.1-adapted vaccine could be a good choice for the next vaccination campaign. This is the end of the presentation. Thank you very much for your attention.

Ms. Hayes: Thank you. Our next OPH speaker is Amy Hart.

Ms. Hart: Good afternoon. I do not have any financial conflicts or interest in this discussion. I'm here to ask the committee to allow anyone to have two COVID shots a year. I'm not over 65 or immune compromised. However, I have multiple comorbidities that put me at higher risk from COVID. The decision of this committee last spring, and the CDC's decision this spring, to not allow second shots for people like me has caused me significant distress. I've met with two different doctors in two different healthcare systems and discussed my medical history. Both have firmly agreed that they would not want me to risk a COVID infection. When asked if they could give me two shots a year, however, both have said they don't have the power to do that. The system administration forbids it because you forbid it, even though vaccine efficacy wanes quickly. Why is the federal government denying me access to a safe, inexpensive, and widely available shot that my doctors want me to have? People tell me to just go to a pharmacy and claim to be immune compromised to get a second shot. I ask them, why should I have to lie and compromise my integrity to receive appropriate medical care? I am not asking for fentanyl; I'm asking for a COVID shot.

In fall of 2019, an unknown respiratory pathogen landed me in the ICU and nearly killed me. My fear of COVID is not hypothetical, and it's not even dying that scares me. I fear long COVID because two of my comorbidities are similar to long COVID. I have a long history of disabling flare-ups resulting from respiratory infections. I still wear an N95, but it's not enough. I need multiple layers of protection from this highly infectious virus because no one layer is perfect, including this shot. However, I cannot wear a mask during a dental cleaning, and I don't think a mask is sufficient during massage therapy when my therapist's face is literally inches away from mine and I find it hard to maintain a good mask fit when she's working on my back.

Because you only allow me one shot a year, I get that shot in the spring. I live in Minnesota and winters are tough. Spring is when I start engaging in more activities that expose me to other people. So I've stopped going to my fall teeth cleaning, and I don't go to massage therapy if COVID is more active, and I've not been vaccinated within six months. So your decision to deny me two shots a year, that's impacting my medical care well beyond COVID.

My fear of engaging in activities that would bring me into contact with others this winter left me isolated and depressed. Your decision has significantly harmed my mental health and I don't understand why you are harming me this way, when you keep saying the shots are safe. Or are these shots not as safe as you claim, and I'm at greater risk from a COVID shot than I am from a COVID infection? Your prohibition on second shots only makes sense to me if there is an unstated risk to these vaccinations. To be clear, I'm not asking you to advise the general public to have two shots a year. I'm simply asking you to say that anyone who believes that they are at greater risk from COVID can work with their doctor to get them. Very few people will pursue this of course, but those who do will be people like me who are at higher risk. By allowing us to self-select for two shots, you can have more impact, at less cost, than trying to convince a broader uninterested public to get a second shot. Thank you.

Ms. Hayes: Thank you for your comments. Our next OPH speaker is Don Ford.

Mr. Ford: Hello, my name is Don Ford. Hello, my name is Don Ford. I have no conflicts of interest. I have a slide. Okay, thank you. My name is Don Ford. I have no conflict of interest. Next slide. The committee is facing a more complicated decision than usual. Mutational jumps are bigger and faster than ever. Imprinting is now a concern, and uptake is very low. Next slide. BA286 really changed our entire position, but first off, I apologize for the graphic. Just imagine the red box on the right is a bit lower. Ultimately, BA286 and its lineages have become dominant

and BA286 became a much more advanced variant than one with just the addition of a single mutation. Next slide. As has been mentioned, choosing the next variant is a significant challenge but everyone seems to agree it's been narrowed down to just a few variants. Next slide. I have three different charts on this slide, but the focus here is not on the variants themselves but the speed at which the variants evolve. These are variants that evolved and became dominant in just a few weeks. No matter what vaccine target is picked today, it will still be behind, based on how fast these variants are moving. And it only takes a single mutation to potentially change the landscape completely. Next slide.

Ms. Hayes: Can you speak up a little louder?

Mr. Ford: Sure.

Ms. Hayes: Thank you.

Mr. Ford: Sure, is that better? Can you hear me now?

Ms. Hayes: Much better, thanks.

Mr. Ford: So, the point was, no matter what vaccine target is picked today, it will still be behind based on how fast these variants are moving and it only takes a single mutation to potentially change the landscape completely. It's important to remember that all these variants have the same immune evasion to XBB antibodies but also to each other, which suggests they're disrupting immune imprinting, which is the foundation of both hybrid immunity and the deeply flawed natural immunity theories. Next slide.

Immune imprinting is an issue that the committee has been facing for some time now, but we actually have to deal with it and things are a bit of a mess. We're dealing with this essential coronavirus which makes it unethical to rely on infection-based immunity, but folks need at least two exposures to an antigen to update their memory response. While infection-based immunity

can technically be considered an exposure, high variability in variants makes it unclear which variant infected a person, making it uncertain if a person's memory response has been updated. Next slide.

The WHO antigenic cartography, which was shown earlier, demonstrates the relative distance from most major variants as well as SARS-CoV-1. As it was already demonstrated, the JN.1 variants are very close to each other, but note the distance between BA1 and BA5. Next slide. Since we're discussing needing two shots to overcome imprinting, then we should discuss the potential of Matrix-M, the Novavax adjuvant, to shrink antigenic range between future JN.1 variants. And since we can establish relative distance between all variants, we can assert with ease that matching Novavax with two JN.1 updates will shrink range to reach the variants we can't see right now. With the speed the new variants are evolving, we need to consider aiming for what we can't see. Next slide. The case for targeting JN.1 has already been made, but we need to think about imprinting because of the significant jump to JN.1 while maintaining an ethical policy. Next slide. KP2 and three are dominating globally, but the prediction that KP3 will be the next dominant variant in the U.S. is not significantly represented in the current data. We see KP3 as a prediction. but we see JN.1-16-1 as a reality. But I was surprised to hear that it was considered a K22-like variant by the CDC earlier in this call, even though it has fewer mutations. There are a number of negatives for choosing a KP variant, but the important factor to point out is that both vaccine platforms require two shots for a proper imprinting update. Next slide.

There's been talks in the past about gaps with RNA protection for reasons that were unclear, but Novavax has a pattern of use that allows for more consistent protection. Currently, the CDC allows for access via immunocompromised standards, but these are confusing both for pharmacists and the public. I hope we can remove the red tape for this timing. Next slide. IgG4 is

a concept that needs more attention and is likely responsible for the RNA protection. But my concern today is that we confirm initial exposures to SARS-CoV-2 vaccines increase that response. And what the committee needs to consider in the future is timing for our regular childhood vaccines, and our COVID vaccines, should it be the child's first exposure of SARS-CoV-2, that it might inhibit uptake of other vaccines taken in that time frame. The last thing we want is our measles vaccine being less effective and I need to point out that the humans gained the IgG4 response after they separated from mice and macaques evolutionarily, so we need human data on this. Next slide.

If we're going to be discussing pediatric vaccines and the concerns of IgG4, then we need to have additional pediatric COVID vaccines at the table. Next slide. JN.1 is the right choice for an update. Please allow for two shots to update memory response. Please shift to an optimal timing to schedule for Novavax. VRBPAC should consider meeting to discuss variants every six months, as RNA likely needs more frequent updates. And Novavax should present data about whether to update or offer an additional dose. Not only are we starting a new wave in the states right now, this will also help our friends in the global south who have their winter while we have our summer. Should the committee decide to go with the KP variant, then please don't let it limit Novavax from bringing its JN.1 update to market as we need a protein-based alternative. Thank you.

Ms. Hayes: Thank you, Don, for your comments. Next OPH speaker we have is David Wipen (phonetic).

Mr. Wipen: Thank you. I had no conflicts and thank you also to my colleagues. Next slide, please, number two. The rise in early onset cancers and COVID-era cancer deaths is widely recognized. Next slide. In testimony to the Texas Senate, we showed extreme event deviations in

UK and U.S. cancer death rates, and all decade cohorts except the mid-50s. Next slide. Delayed screening and lockdowns could partly account for this. With plausible mechanisms we cannot exclude coronavirus or vaccines. Next slide.

FDA testified to a House committee; we have not detected any increase in cancers with the COVID-19 vaccines. This ignores CDC's own safety signals to 16 cancer codes, pending causality determination. Slide seven. And neglects a growing number of case reports. These signals are absent from recent reports from FDA, CDC, and the National Academies, and are inconsistent with FDA's letter to Florida's Surgeon General and Pfizer's letter to a South Carolina Senate committee. Next slide. The COVID and RSV mRNA vaccines were not tested for cancer effects. FDA's summary cited in the letter omits a genotoxicity study showing increased micronucleation. Next slide.

We expect residual DNA as a process-related impurity, but we found levels approaching guidelines when measured by PCR, known in Moderna's patent to underestimate DNA. Fluorometry levels well exceed guidelines, which do not account for enhanced transfection by lipid nanoparticles. Next slide. DNA exceeds size guidelines cited but not enforced by FDA, as Pfizer claims to Health Canada. Next slide. With plausible oncogenic mechanisms not requiring insertion, integration risk is acknowledged by Moderna, BioNTech and FDA. But FDA trivializes this in its Ladapo letter, by positing DNA's inability to cross the nuclear membrane. The same chapter, FDA cites, describes this membrane dissolving during mitosis, along with FDA's argument. Next slide. Comirnaty contains SV40 regulatory sequences that Pfizer chose not to disclose per Health Canada, omitting them from the plasmid map sent to EMA. Claimed to be nonfunctional, these sequences have plausible tox mechanisms. As guardians of public trust, where is FDA's censure of Pfizer? Next.

Our work has been variously replicated and continues with preliminary evidence of residual DNA integration, in cancer cell lines and replication, at least episomally with mutation, along with an exploratory dose response effect to residual DNA and serious AEs. Next. Alarmingly, a UK MRC group found frameshift proteins and off-target immune responses evoked by error-prone mRNA, with a, quote, huge potential to be harmful. The small select cohort affords no safety assurance, and an email shows concern in Health Canada. Next slide. Adding to unknown mRNA and spike kinetics dismisses academic at VRBPAC two years ago, frameshifting represents uncontrolled pharmacology of uncharacterized proteins of unknown toxicity, whose production must be disclosed in the label. The last slide.

Pfizer's former research head boasted flying a plane while still being built. It's time to ground the plane. The EUA evidentiary standard can justifiably read, based on the totality of evidence, it is reasonable to believe that the product may be unsafe. FDA must investigate cancer signals, correct house testimony, regulatory documents, and letters to health officials. FDA must release DNA data, revise, and enforce guidelines, and censure companies who betray public trust, while supporting scientists who seek to further trust in science. You know where to find us. Thank you very much.

Dr. Hayes: Thank you. Our next OPH speaker is Mark Gibbons.

Mr. Gibbons: Hi, I'm Mark Gibbons. I have no conflicts. I'm the president and CEO of Retire Safe, a nonprofit organization focused on the concerns, needs and opportunities of older Americans. In my lifetime, the concept of retirement has changed significantly. For many, it is now a time to begin a new career. For others, traditional retirement is elusive. Economic and family necessities require working well beyond one's mid-60s. Recognizing this shift, our organization has increasingly focused upon health as well as economics, as twin pillars of

retiring safely. That is why I appreciate the opportunity to speak today. The COVID pandemic dramatically challenged our concepts of public safety. But thanks to the work of brilliant and dedicated scientists from government and private industry, our public and private health systems, agencies from every level of government, including this very agency, our life is back to normal, almost. We now understand quite clearly how much of our health and safety relies on prevention and access to timely treatment.

We know now that COVID is an ever-present and ever-changing part of our lives. And we applaud FDA's work in developing an updated vaccine to help our bodies fight the newest and most concerning COVID strains, as has been done for so many years to combat the flu. Retire Safe will also be urging CDC to make its recommendations for the 24-25 COVID vaccine as quickly as possible so that it will be available at the start of the season, when older Americans are already focused on getting protected for the upcoming respiratory threats like the flu. We know, from well-documented statistics, about the age cohorts we serve, that older adults can be counted upon to take advantage of the protections offered by immunizations, and that all of us benefit greatly from making it easy and convenient for everyone to access vaccines that protect us from respiratory diseases. We do, however, need clarity for ourselves and for our providers who care for us and treat us. We want to be sure we understand who gets what and when. We hope decision makers will keep in mind that we are incented and more responsive when we can access important vaccines where and when it is most convenient. These considerations are critical to addressing the health needs of millions of men and women.

We appreciate and applaud the careful and truly life-saving work this agency performs, as well as the expertise and contributions of this committee. COVID vaccines are essential to

keeping us safe and healthy. COVID vaccines that better protect us from current strains are of great benefit. Access early is a win for everyone. Thank you for your time.

Ms. Hayes: Thank you, Mark. The next OPH speaker is Burton Eller.

Mr. Eller: Thank you. Good afternoon, and we have no financial conflicts to report. I am Burton Eller with the National Grange, an organization in its 158th year of service to rural America. Grange is unique in that it supports all aspects of rural life, from farming and ranching to youth programs, from increasing access to technology to improving health access and education. Working through more than 1400 chapters throughout the country, Grangers support and advance the well-being of their fellow members, their neighbors, and their communities. Our work in health education and advocacy stems from the well-known fact that rural citizens face many disparities. Access to care is more difficult because there are fewer clinicians, far fewer medical specialists, and increasingly fewer hospitals, combined with the need to travel greater distances to get care.

The onset of COVID presented us not only with many of the same difficulties facing urban and suburban Americans, but also a number of obstacles unique to small communities and regions with limited access to health care services and supplies. As it has in the past, Grange together with the state and local chapters stepped up to help schedule vaccine opportunities and disseminate education materials. Even as the pandemic waned, Grange has continued to provide opportunities to rural America to receive COVID and other vaccines to protect their health. A great example from last fall took place at the legendary Big E Fair, a decades-old tradition that was organized by all six New England states many, many years ago. It ran from September 15 through October 1. Over 3,500 COVID and flu vaccines were administered by licensed pharmacists and nurses at this event. I'm highlighting this event for two reasons. First, the state

Granges who participate at the Big E are proud to have been able to provide this community service. The clinic was also paired with the Grange McCoy funded project to improve surgical outcomes by providing free and post-operative care information to rural seniors. A second reason to call it to your attention relates directly to the access issues facing rural America. We were only able to get COVID vaccine at the very last minute because of the timing sequencing involved in the approval and recommendation of that updated COVID booster. We made it by September, but barely. This prospect of having a vaccine specific to COVID virus strains expected to be prevalent this fall, in time for the beginning of the respiratory season, is a welcome advancement, one that can help us stay healthy this fall and winter. Access for rural Americans is not as simple as going to the corner drugstore, doctor's office, or local hospital vaccine clinic. Corner drugstores are few and far between. While 20% of Americans live in rural areas, only 9% of physicians practice there, and since 2010, 136 rural hospitals have closed. It is so very important for rural families to be able to make the most of their trips for groceries, for supplies, for recreation, and for health care. Trips cost dollars and time, both of which are often in short supply. Making a safe and effective COVID vaccine that protects us from this year's virus versions can best serve rural populations when it is easily accessible, such as when a family gets the yearly flu shot. We thank FDA and the experts on this panel for their expertise and wisdom in reviewing a COVID vaccine for the start of this season, and for their consideration of the circumstances that impact rural living. Thank you.

Ms. Hayes: Thank you, Burton. Our next public speaker is Sue Peshin.

Ms. Peshin: Thank you. Good afternoon. I'm Sue Peschin and I serve as the President and CEO of the Alliance for Aging Research. The Alliance is one of three co-conveners of the COVID-19 Vaccine Education and Equity Project, or CVIP, a collective of more than 250 nonprofit

organizations that are focused on equitable access to vaccines and treatments. Both CVIP and the Alliance receive funding from sponsor companies, but we do not advocate for any particular vaccine.

First, thank you to the FDA and to this advisory committee for meeting early enough to allow these updated vaccines, if approved or authorized, to be available in August on a time frame similar to annual flu vaccines. In 2023, the public, including all those at highest risk of hospitalization and death, didn't start getting their COVID-19 vaccines until over a month into the respiratory season, and after 83 million flu vaccine doses had already been administered, according to CDC. Unfortunately, that was a missed opportunity to ensure more individuals could vaccinate for COVID-19 and flu at the same time. That said, we are thrilled and grateful to see the coordinated steps taken between the FDA and CDC to better align with the start of the 2024 respiratory season, so thank you. And for today's discussion, we want to put our full confidence in the FDA's expertise on strain selection and vaccine technology. The FDA acknowledged in today's briefing documents that there are differences in production timelines between mRNA and protein-based vaccines, with the latter taking longer. However, in addition to timeline considerations, we know that there are people living with rare diseases and compromised immune systems who require protein-based vaccines, so please keep that in mind as you consider how strain selection will impact the availability of different types of vaccines, so that all members of the population can be as protected as possible. And more broadly, here's what we're seeking today.

The FDA and CDC must use clear and simple COVID-19 vaccine recommendation language that's as easy to implement as possible. Age-based routine recommendations six months and older are critical, so that there aren't delays or confusion in who is eligible for the vaccines.

For CDC, please avoid shared clinical decision-making recommendations, which impede access, as we've seen with pneumococcal vaccines and are also seen with the RSV vaccines. Both agencies must also craft simple and consistent messaging on co-administration of vaccines. For example, is it okay for my 83-year-old mom to get the updated COVID-19 vaccine when she gets her annual flu vaccine? What about co-administration and timing for the RSV pneumococcal, or any other recommended vaccine? We also implore both agencies to emphasize the benefits of enhanced flu shots for older adults and to amplify the recently published research in JAMA on the life-saving benefits of RSV vaccines. We need to push those who make the big decisions on access and payment to give everyone a fair shot at protection this year. And to the Centers for Medicare and Medicaid Services staff that may be listening today, CMS must fix long-standing payment issues for vaccine administration in long-term care settings. If skilled nursing facilities and pharmacies had the ability, which they should, to confidently vaccinate anyone in their purview at any time, and know they'd be reimbursed appropriately, we would see a significant uptick across all recommended vaccines. And this also applies to long-term care staff. During COVID-19, many staff were vaccinated alongside the residents during the clinic days at the nursing homes, but that flexibility is long gone. As the saying goes, those who forget history are condemned to repeat it. Thank you to this advisory community for serving as true advisors to the FDA, and for respecting and supporting the FDA's and CBER's deep expertise in vaccine review. We have a long way to go together to repair years of misinformation on vaccines, the FDA, and the important process that you're participating in today. So, thank you very much.

Ms. Hayes: Thank you. Our next OPH speaker is Thair Phillips.

Mr. Philips: Hello, I'm Thair Phillips, and I have no conflict. I'm the national spokesperson for Seniors Speak Out. The name of my organization is well chosen because it is our goal to

encourage older Americans to be vocal about their concerns regarding our healthcare system, the policies that govern it, and the limitations and possibilities that impact its ability to provide the care we need. It is why we are here today. Older Americans are major healthcare consumers. That's no surprise. But it should also be noted that we are often in the forefront of modeling good healthcare practices wherever and whenever possible. Consider, for example, how quickly and in what numbers we showed up on time and willingly stood in line to get our shot when COVID vaccines first became available. Follow-up surveys report that 95 percent of U.S. adults over 65 have received at least one COVID-19 vaccine, and over 94 percent completed the primary series. But then came the drop-off. Surely, vaccine fatigue and confusion over what we needed over and above the primary series took a toll, but the data show that older adults did show up to get boosters in vastly higher numbers than younger or middle-aged adults. It is imperative that we not only keep up that momentum, but also rev it up to approach the higher levels we saw at the beginning.

I'm speaking out today on behalf of seniors, which is my age group, to ask you to help make that happen. It is very important for public health, and on every level, to help Americans understand that, similar to the flu vaccines, this COVID shot is specifically made to address the COVID viruses that have newly emerged. It's new and improved if you will. That is very big news. People need to know that. And a major step to increase the number of people vaccinated, and specifically the older generation who are most vulnerable to respiratory illness, would be to ensure that the new COVID vaccine is available when we get our flu vaccine this fall. This would eliminate the need to make another appointment at the doctor's office or clinic or set up a time ahead at the pharmacy. These two things, public awareness, and ease of access, can address

two major barriers for older Americans to be able to easily access those important tools for protecting our health and make a difference for us all. Thank you.

Ms. Hayes: Thank you. And our last public speaker, we have Andrew Wang.

Dr. Wang: Hi, everyone. Dr. Monto, Dr. Marks, members of the committee and members of the public, thank you for this opportunity to speak at today's FDA Vaccines and Related Biological Products Advisory Committee. My name is Andrew Wang, and these are my official comments for the record. I'm speaking on my personal behalf as a public health professional and health service researcher, as well as a concerned American. I have a doctorate in public health, a master's in public health with expertise in health disparities and social determinants of health. My primary work is in Chicago, Illinois at an urban-based federally qualified health care center that provides primary care for underserved and vulnerable populations. I also hold an affiliation with an academic school. I'm also part of several national and local public health watchdog and advocacy groups. I have no conflicts of interest and currently have no financial sponsorships by investments in the manufacturers or developers of the COVID vaccines. Foremost, I want to express my appreciation for all of your dedication and commitment to ensuring the health of the American people.

The COVID pandemic has not ended, especially for many Americans, including those with vulnerable health conditions, disabilities, and for all age ranges. Although political interests are trying to pull attention away from that, the scientific and medical community must continue to pay close attention. COVID remains a serious and harmful infectious disease, resulting in deaths, hospitalizations, and long COVID. First, the medical community continues to be aware that any medical device may have side effects and for some adverse events, the FDA committee should carefully examine those affected populations and continue to ensure future vaccines result

in zero harm. Second, the COVID vaccines have ultimately prevented millions of deaths, hospitalizations, and some infections. Therefore, it is even more important to ensure that the COVID vaccines remain at the highest level of effectiveness.

Scientific evidence indicates updated vaccines are needed to address the ongoing changes in COVID variants, and they should ideally be allowed, available, and fully covered by public funds and annual insurance for people of all ages and at least every six months. The vaccine schedule should address waning efficacy in the months following vaccination as well as some emerging new SARS-CoV-2 strains. Today's decision by the FDA will continue to affect the current and future vaccine approach, including what health care providers recommend, what health insurance covers, and poignant levels of public engagement. The current situation regarding the ongoing COVID pandemic is as follows. Wastewater levels for SARS-CoV-2 are rising as per wastewater scan and CDC's Wastewater Surveillance System. Current levels are nearly as high as fall 2023, and the risk of transmission comparatively to low levels are currently at moderate levels. According to the CDC, as of May 24, 2024, the SARS-CoV-2 lineage KP2 is now the primary strain projected to be at 28.5% and the lineage JN.1 is now modeled at 8.4%, no longer the dominant strain. Similarly, as in previous years, when new strains show earlier dominance, they are more likely to grow and become the dominant strain. As we have all observed in these past few years, this demonstrates that JN.1 will continue to wane, and KP2 will be the better target for COVID vaccines, especially if COVID reaches higher levels during the end of summer 2024 or either fall 2024 or early 2025. We have learned that mismatched strains result in quickly waning protective vaccine immunity. It is of utmost importance that the FDA anticipates the newest viral variants and provides recommendations that anticipate the next dominant strain in the next six months. This requires that the FDA ensures that manufacturers not

only anticipate the newest strains but also ensure a vaccine that is more comprehensive for any type of future variant.

The FDA has both the clinical responsibility and the ability to leverage manufacturers to not just chase, but effectively develop a more comprehensive vaccine. Restricting vaccines to only annual updates not only misses an opportunity to address changes in dominant variants, given that there is a potential to update the vaccines to better match potentially emerging variants. Ensuring all vaccine types are needed, and mRNA vaccines are particularly suited for quick updates to match with the most dominant variant while protein-based vaccines have longer duration and protective effects. The recommendation for only an annual vaccination also creates barriers for vulnerable people and discourages a general population from having access to year-round access to the vaccine and much-needed vaccine boosters. Last and most importantly, the FDA must continue ongoing collaboration with the CDC to ensure manufacturers provide equitable affordable access to updated vaccines and prevent limited access to financial constraints, ensuring equitable access through the bridge program and patient assistance programs. Thank you so much for your time today and for your consideration.

Ms. Hayes: Thank you and thank you all for sharing your reviews and comments and participating in today's advisory committee meeting. This concludes the open public hearing session for today, and I will hand it back over to our chair Dr. Monto to move into the next session.

**Additional Q & A For CDC, FDA, and Industry Presenters**

Dr. Monto: We've finished a little bit early and it would be very good if we could return to our discussions that we had before the lunch break. We have an actual break at 2:20, or just a break, so why don't we try to devote our questions now to the CDC presenters and to the manufacturers. And I see Dr. Hawkins has his hand raised. Dr. Hawkins.

Dr. Hawkins: Yes, thanks to the presenters. This is a question about vaccine acceptance and utilization. The effectiveness of prior vaccine was shown in the data presented; there remains persistence of critical illness and non-vaccinated persons, and some that are vaccinated. Not uncommonly, there's community acceptance of coronavirus as a not so severe infection and some vaccination fatigue. If approved, will there be a robust public health push for vaccine acceptance and utilization in the upcoming season including certain populations?

Dr. Monto: I'm not sure who that question is directed to.

Dr. Hawkins: CDC.

Dr. Monto: CDC.

Dr. Hawkins: Did you understand the question?

Dr. Monto: The question is, are they back?

Dr. Wentworth: So, I'm representing WHO on this call, but I am a CDC employee, and I don't see my other colleagues on the call, and I want to try to address that for you. So, I mean, what we're really doing – and this is an HHS program; it's not just CDC. And Dr. Gelles may be able to address the question as well, but I'll start off and if you have improvements to my answer that would be wonderful. So we're really trying to have a campaign, ensure vaccine availability, and have a campaign indicating we anticipate fall and winter season of respiratory viruses. This includes not only COVID, which we've discussed has periodicity but not necessarily seen seasonality, but flu and RSV. And as Dr. Marks has pointed out in the past, what we can anticipate is that fall and winter season to have peaks of respiratory disease. And so the campaigns that we will be having really encourage people to have the information needed to make an informed choice of whether or not they'd like to take the vaccine. All right Dr. Offit.

Dr. Monto: Alright. Dr. Offit.

Dr. Offit: Yes, thanks Arnold. So, I have a follow-up question actually for Dr. Link-Gelles, so thanks for being back on, Ruth. You had stated that you don't have to be in a high-risk group to be hospitalized or die from this virus. And it's while it's certainly true that for children; we see children in our hospital who are hospitalized, less than 18 years of age, often less than five years of age, but the main reason for that is they're not vaccinated. So I certainly agree that everybody needs to be vaccinated. I'm trying to understand this: let's say for the healthy 25-year-old, or 30-year-old, who got a primary vaccine series, got two or three doses of the Wuhan one strain, or two doses of Wuhan one and a natural infection, but didn't get vaccinated last year, didn't get vaccinated the year before. Are they still protected against severe disease? Because you could argue that they still are, to the extent that they have memory t-cells, especially cytotoxic t-cells, that are recognizing conserved epitopes, that even though they were only vaccinated or naturally affected with an earlier strain, are still protected. Are those people getting hospitalized? Are healthy people who've been vaccinated or naturally affected or both, who are not in high-risk groups otherwise, getting hospitalized to a degree that it makes sense to recommend this vaccine for everybody over six months of age, remembering that only we in Canada do that. All the other countries are targeting high-risk groups. So, help me with this, Dr. Link-Gelles.

Dr. Link-Gelles: Sure, so, for this year it's been not enough time yet to say truly how long the 23-24 vaccine lasts. What we know from the original monovalent vaccine and bivalent vaccines from past years was that protection against hospitalization including in the 18 to 49 or 18 to 64, so younger adults, without immunocompromising conditions, protection against hospitalization waned over the course of the first year or two years. And the protection by the end of a full year out from a vaccine, against hospitalization, was about zero. Now, you could talk a little bit about how many of these people are being hospitalized for versus with COVID, but certainly there is a

proportion of them that are being hospitalized for COVID, or for exacerbation of asthma, or something like that, so not a true immunocompromising condition, that would qualify you for extra doses. So we know that vaccine effectiveness against hospitalization does decline over time, and so that there will be benefit even to younger adults to get an updated vaccine. Now, again, we do know that vaccine effectiveness is more sustained against critical illness, and so that there is some protection remaining, probably, from the bivalent and original monovalent vaccines. Although even that does decline somewhat over time, just not as much as against hospitalization.

Dr. Offit: So, sorry one quick follow-up and then I'm done, Arnold. So that Mark Tenforde paper, you came out of the CDC, publishing clinical infectious disease. We made the case then, that was like end of 2022, that it was really mostly those high-risk groups, you know, being immunocompromised, with medical conditions, pregnant, or chronic, or a large number of comorbidities. Those were the ones who predominantly were getting hospitalized. But you're saying there's a significant number of people, young, healthy, have been vaccinated, even with older vaccines, that are getting hospitalized or dying?

Dr. Link-Gelles: Well, so I don't have the exact numbers in front of me. Our vaccine effectiveness networks are not nationwide. We're not the COVID network that does the larger epidemiology of COVID, and that will be presented at the ACIP meeting in late June, where they'll do a deep dive into the epidemiology. I will say, even in our paper that you mentioned, there were people in that study that had received prior doses that otherwise appeared to be healthy, that did end up hospitalized. So it's not that it never happens. It is certainly more common amongst those with underlying conditions, in particular immunocompromised and so on, but we do see hospitalized individuals that are otherwise healthy and younger adults.

Dr. Offit: Okay. Thank you.

Dr. Monto: Dr. Sawyer.

Dr. Sawyer: Thanks. My question is about vaccine supply. We've heard from each of the manufacturers that they can assure us supply adequate to meet demand, but we don't yet have the ACIP recommendations for how this new version of the vaccine will be used, so I'd like to hear either from the manufacturers or perhaps someone at CDC has already discussed this with the manufacturers. Is their projection about availability based on the current use of the 23-24 vaccine, to boost high-risk people and to use as a primary vaccine in those who have not already been vaccinated? And is the supply projection throughout the season, or is it going to be available let's say by December? Since we've learned over many years that people stop getting their flu shots on January first, and I suspect the same may happen with COVID. So I'm not sure who to direct the question to, but I'd like to hear a little more about that.

Dr. Monto: Anybody from CDC ready to respond?

Dr. Wentworth: Hello. Again, I think, as far as vaccine availability, we heard from the manufacturers what that's going to be, so I won't comment on that. I will comment on the recommendation for additional doses - that is from the ACIP working group and they previously had recommended that those in high-risk get additional doses, but those with immunocompromising conditions can get additional doses on top of a single additional dose, every two months. And I think that was in one of the public comments. You can self-identify as somebody that needs additional doses and being moderately immunocompromised. So that's that. And then what was another part of your question? I kind of forgot.

Dr. Sawyer: Well, I mean it's all related to just what you said. If you don't expect that recommendation to change, then I assume the manufacturers are estimating the supply that they

need to provide, based on that recommendation. So that's helpful. And then the second part of my question is really the timing. Is, when they say they're going to have enough vaccine, does that mean between August and April, or is that between August and December? Or can they tell us that?

Dr. Wentworth: My real closure was discussed, but I'm going to leave it to them to describe.

Dr. Monto: And, Dave, vaccine supply hasn't been an issue.

Dr. Wentworth: Recently… it's been utilization, correct?

Dr. Link-Gelles: Yeah, and this is not really a question for CDC, so maybe we can redirect it to the manufacturers.

Dr. Sawyer: But has supply been an issue?

Dr. Link-Gelles: Well, we did see last season, with the early part of the rollout, that even though we had vaccine available sometime around mid-September, that people were reporting anecdotally not being able to find it or having delays getting appointments. There were some temporary insurance concerns as well, and things like that. So I think I wouldn't say it was necessarily a concern because it corrected itself within weeks, but during those early weeks some members of the public expressed frustration of not being able to get the vaccine when they wanted it, which is certainly a deterrent for returning at a future point to see vaccination again.

Dr. Sawyer: I guess I partly asked the question in the hopes that we're going to get more uptake than we've had in the past, as we sort of normalize COVID vaccination and move into this once-a-year updated version. So the past experience may not predict what happens this fall.

Dr. Monto: Yeah, we all wish we would have more uptake. It would solve a lot of issues. But is there a response from Moderna? I see your hand raised.

Mr. Priddy: Yes, thanks. And maybe to clarify the statements that we made during our presentation, so we do project that we will have the supply that the market needs, upon launch as well as through the season. Our projections are partially based on the supply that was needed last season, but also incorporates ongoing discussions with retail pharmacists, with doctors, with health agencies, and medical systems. Now, in terms of exactly what we would expect, in terms of need, that could change based on when the approval actually happens. If the approval happens coinciding with the flu season, that could, hopefully, increase uptake, as more co-administrations might happen. But that is actually built into our projections, you know, a launch coinciding with the flu season.

Dr. Monto: Thank you. And I see a hand raised from Pfizer. And from Novavax.

Dr. Modjarrad: Thank you. As we mentioned earlier, regardless of whether a JN.1 or KP2 vaccine is selected, we will have sufficient supply available, for either vaccine. With respect to the timing of the supply, I'll ask again my colleague, Dr. Falstich, to provide additional details.

Dr. Falstich: Hi, good afternoon again. Bill Falstich, vice president of global supply chain here at Pfizer. So, just to answer the question, we have modeled demand based on our prior experience, based on our negotiations with customers, and discussions with customers, and then based on analogs such as flu uptake. We project that based on the demand we have modeled we'll be able to supply in all periods, starting as early as August or upon approval. We're preparing for an August approval but of course that's subject to regulatory review and timelines. And we would maintain that supply for as long as it's needed, so through the end of the year, and then into the 2025 season as well, is what we would anticipate doing.

Dr. Monto: Thank you. And Novavax, please go ahead.

Dr. Walker: Yes, thanks. Rob Walker, Novavax. As mentioned during the presentation, we are manufacturing JN.1 vaccine. We anticipate no constraints, and that we would be able to meet projected demand, and we are projecting to have that available, as mentioned, September one.

Dr. Monto: Thank you. Thank you, all. Dr. Jansen.

Dr. Jansen: Hi, this is a question for Dr. Link-Gelles about surveillance. So, it seems now that surveillance is symptom-based; you're describing the tip of the iceberg. And in the early days the placebo arms and controlled vaccine trials gave an estimate of that. Do you know if there's any work that's being done now to give a sense of the proportion of infections that are asymptomatic now, especially with effective vaccines, compared with the past? And then the follow-up to that is, your vaccine effectiveness estimates, in my mind assume the proportion of asymptomatic infections is the same between COVID and other respiratory infections, which may or may not be true, because my guess is that your answer to the first question is no. So do you think your vaccine effectiveness estimates may be over or underestimating VE?

Dr. Link-Gelles: So, to start with your first question on surveillance, I will preface this with I'm a vaccine effectiveness expert, not a surveillance expert, and those folks are not on the line today, but you know over time we had at the beginning of COVID a number of studies that did routine swabbing of individuals enrolled, which is what you would need to get at that question. And so every week folks would do a home swab and submit it, whether or not they had symptoms. And that allowed us to look at the proportion of people walking around with asymptomatic COVID that didn't know that they were infected. Those studies are incredibly resource intensive and there's diminishing numbers of people in the population that are willing to participate in a long-term study like that, so they're relatively uncommon these days. So I think it's pretty hard to get at the number of asymptomatic people as you suggest. To your vaccine effectiveness question, I

don't think that those proportions would have an immediate impact on our VE estimates. So the way that we enroll in our VE studies is to take people with symptomatic COVID-19, and that is done specifically to get around bias in who's getting tested, so you would have two similar people that show up at an emergency room or an urgent care center or a hospital, with similar symptoms, and then test them. And so potentially there are still healthcare seeking issues that could creep in there, and certainly when we don't have universal testing in hospitals and emergency rooms like we used to for COVID, there can still be biases in who's tested and who's not tested. But I don't think that the proportion that are asymptomatic would contribute greatly to that at this point.

Dr. Monto: Thank you. Dr. Berger.

Dr. Berger: Hi, so I actually have two questions, and hopefully they're very quick. The first one is to Novavax. You know, specifically you talked about the fact that if it's not a JN.1 vaccine composition, that there won't be a protein-based vaccine available come fall. And I wanted to better understand what the limitation is here. Is it simply time, is it the timing of these meetings and when decisions are made and what the composition needs to be, or is there something else? Because it’s a potential outcome of what the FDA might decide to do, after they hear from us. The second question that I have is specifically to Dr. Ruth Link-Gelles, and it gets into the vaccine efficacy question as well. I also had a question just on the symptomatic infection rates, mostly because in that actual data you combined everyone above 50, all together, and just wanted to understand if there was any differentiation for those that are above 65 when it comes to vaccine efficacy. Thanks.

Dr. Monto: So, let's hear from Novavax first, to the question.

Dr. Walker: Yes, Robert Walker, Novavax. Thanks for the question. Yeah, it's an issue of timing. The protein vaccines, as you're probably aware, are complex biologics with extensive regulatory safety and quality requirements during manufacture. We stated last year at the VRBPAC meeting that it generally requires six months for manufacture, and that is in line with influenza vaccine production. So it's really no other factor, to consider.

Dr. Monto: Thank you. Dr. Link-Gelles.

Dr. Link-Gelles: Sure, so in the ICAT data we generally lump everyone 50 and up together, because what we've found is that those 65 and up don't seek testing at pharmacies nearly as often. They're much more likely to try to see their own provider or go to an urgent care location. And so if we try to split into more granular age groups above 50, we lose statistical power very quickly. So unfortunately, there's not really an ability to split that out.

Dr. Monto: Thank you. Question from Dr. Meissner.

Dr. Meissner: Thank you, Dr. Monto. I would like to follow up on a comment from Dr. Hawkins. I don't think anybody can accurately make an argument that there hasn't been an enormous benefit from the messenger RNAs, since they've been introduced. It's been extraordinary. But I think the setting has changed pretty dramatically, in terms of hybrid immunity and the severity of disease that we're seeing. And so, while the overall benefit to public health has been enormous, I think the question that many people are asking is whether the benefit to certain individuals depends on their risk of exposure, and the severity of disease in that age group. And I just note the data that came out of the CDC as of last March 20 of this year, only about 25 percent of people over I think it was 18 years of age had received the updated 2023-2024 vaccine. So, I just worry about the strength of the recommendation that's going to be made, because I think if the CDC makes a recommendation that people are simply not going to follow,

that's harmful for the overall immunization program. And I hope that it's possible to take that into consideration, because I think, listening to the data that's been presented so far, I think a good argument can be made to updating the vaccines. But I just worry that an overly enthusiastic endorsement may not be in the best interests of the immunization program.

Dr. Monto: Noted. Dr. Chatterjee.

Dr. Chatterjee: Thank you, Dr. Monto. This will be a good follow-up to Dr. Meissner's comment. So, I have one comment and a question. And the question is for the CDC folks, colleagues that are here, perhaps they can answer the question. But I'll make the comment first. And I'm sure you all are hearing this, seeing this, reading about this, I think we're talking about the same issue about uptake, and the perceived risk of COVID-19. Of all the data that were presented today, the one slide comparing influenza burden of disease and mortality to COVID really spoke to me. If we are able to highlight that, to help the public understand, my biggest concern is that I'm hearing from physicians, from public health officials, who seem to have become blasé about the risk of this disease. So, this is just a comment and I guess a word of caution to all of us, to think critically about how we can collectively help people understand that this is still a very serious problem. The question, for the CDC folks, is regarding timing of vaccination. Given the data that were presented in terms of waning immunity and vaccine effectiveness being much lower once you're a couple of months out from vaccination, I am wondering, even though we expect the vaccines to be available August-September time frame, whether it may be more prudent to delay vaccination for, at least for some groups, that might benefit from waiting until we start to see the increase in cases occurring, and have some understanding that we are in a new season if you will, of the infection. And perhaps then the immunity would last a little bit longer. So, just a thought and a question for the CDC folks, if anybody can address that.

Dr. Monto: Dr. Chatterjee, they say it's not like flu, but in some ways it becomes more and more like flu.

Dr. Chatterjee: I agree with you. I think it is going there. I think it isn't there yet perhaps, but I do think in the public's mind at least, that this may be how they're viewing it.

Dr. Monto: Yeah I understand, and I think people are beginning to think about timing of their vaccination because of the recognition of waning. Dr. Link-Gelles.

Dr. Link-Gelles: Yeah, I was just going to say I think you know it's very difficult to talk about timing COVID-19 vaccines for the respiratory virus season. For flu and for RSV we have years and years of data with very similar trends over time, so, you know, you can't quite set your watch by when those seasons are going to start, but you can get close. For COVID that's not true at all, we've seen surges in the summer, in August the last few years, and so I think, you know, it becomes a little bit of a difficult game to try to play to time COVID vaccine introduction right before a surge. I think the other important point to keep in mind is that when we've seen COVID surges before, they're often, you know, with quite a peak, rather than sort of a large span of time. And so, to put in place a recommendation rollout vaccine and get people vaccinated in time, and then they need about a week to two weeks to really have the full benefit of the vaccine, we would risk kind of missing that peak. And so, for those two reasons I think it's very difficult to try to time COVID vaccine before an oncoming surge. And so I think what we're left with is trying to time it with the respiratory virus season and think about uptake at the same time as folks are getting their flu vaccines.

Dr. Chatterjee: Points well taken.

Dr. Monto: This will resolve itself over time, when we begin to see more COVID seasons, which clearly are going to keep happening.

Dr. Chatterjee: Yeah, I was just wondering, Dr. Monto, if I could ask a quick follow-up question?

Dr. Monto: Okay, very quick.

Dr. Chatterjee: Very quickly.

Dr. Monto: We'd like to get to the bottom of our list.

Dr. Chatterjee: Yeah, very quickly. This comes from some of the comments we heard during the open public hearing, and that is about, so, let's say we start the vaccination program August, September, whenever we start, and the peak really doesn't happen until several months later. Would there be an opportunity for those who were vaccinated early on to get another dose of the vaccine once we start to see that uptake? Particularly if they had underlying health conditions that would put them at high risk for hospitalization and more critical illness.

Dr. Link-Gelles: I will defer that question to the ACIP conversation at the end of June.

Dr. Chatterjee: Thank you.

Dr. Monto: Thank you. The last response that we had from ACIP was a bit confusing, so I hope things are a little clearer the next time. Dr. Meyer.

Dr. Meyer: Yes, and not to perseverate too much on the supply and distribution discussion, and return to that, but I did have one follow-up question because a number of the manufacturers said they would be ready to go upon FDA approval or authorization. And so, I think just to round out that line of questioning, I did want to ask FDA if the particular strain selected, JN.1 versus KP2, has any impact on the timing that FDA would be able to approve or authorize the vaccines?

Dr. Monto: Dr. Weir.

Dr. Weir: Yeah, so I can partially address it, but I think you'll have to get the manufacturers to chime in.

Dr. Monto: We're not going to do that. We're almost out of time. Go ahead, please.

Dr. Weir: Well, our ability to review and act on it will depend on when all of the necessary data is submitted, and the manufacturers may or may not be able to submit the same amount and quality of data for one variant as another, at exactly the same time. That's what I meant, about, you might have to ask when they would be able to submit data to the FDA. But that would be the only limiting factor. But it would be relatively minor in the scheme of things as far as timing. Over.

Dr. Monto: Yeah, we'll do that after we have our discussion if we have the time. Dr. Gellin.

Dr. Gellin: Yeah, thank you. This is a science question, and probably not a practical question, for what we've been talking about. The two mRNA manufacturers have candidate vaccines for both JN.1 and KP2. Have they looked to see what the immunogenicity and reactogenicity of a bivalent would look like?

Dr. Monto: I'm going to rule that out of order, because that's really not something we're discussing today. If we have time, we'll come back to that later on. Dr. Levy.

Dr. Levy: Thank you. Several of the people who have raised some points in the past half hour have brought up the question of relatively lower risk, for children, of severe COVID, which is certainly true and notable. Another way to think about this, and this will be a question for CDC, is by analogy to other infections. We give meningococcal vaccine to infants and children in hopes of preventing rare but very severe cases of meningococcus, you know maybe 100-200 deaths a year in the United States, and we recommend a blanket immunization, routine immunization of children for that. And another angle to think about it, this is the other question for CDC, is long COVID. The presentations went by a bit quick, but does CDC have a sense of whether the current vaccines are showing any VE vaccine efficacy against long COVID,

including in children? So those are my questions to CDC, have they looked at the data in that way, in relation to a rationale for immunizing children.

Dr. Link-Gelles: Sure, so to your first question, yes we've absolutely compared the rates of severe disease and death in young children to other vaccine-preventable diseases. For that I would refer to a couple of recent ACIP presentations given by Megan Wallace and Sarah Oliver at CDC. And I would imagine that some form of that analysis will also be included in the ACIP presentation later in June. And then, I'm sorry, on your second question, could you repeat that?

Dr. Levy: Any evidence of vaccine efficacy of the current vaccines against long COVID in adults and children?

Dr. Link-Gelles: Yeah, so, you know, vaccine effectiveness against post-COVID conditions is particularly hard to study because it requires both knowing that someone was infected or not infected, and then having adequate follow-up time to look for post-COVID conditions. So, I'm not aware of recent data from this current season's vaccine showing effectiveness against PCC, post-COVID conditions, or long COVID, but there is quite a bit of data from prior iterations of the vaccine showing that it does provide some protection against long COVID.

Dr. Levy: In children as well?

Dr. Link-Gelles: Correct.

Dr. Levy: Yeah, and so that would form another rationale for immunizing in early life. Thank you.

Dr. Monto: Thank you. Finally, Dr. Bernstein.

Dr. Bernstein: Thank you. I'm hearing a lot of different opinions around the table as far as vaccinating children and as well as other populations, and I am concerned that our universal recommendation at this point for a COVID-19 vaccine for everyone may be a detriment to the

overall vaccination program. And I definitely feel we need to emphasize vaccinating the unvaccinated more, so and I'm not sure in what direction we go. And you keep saying, Dr. Monto, about looking more and more like flu, and I do remember that years ago influenza recommendations were risk-based and migrated or transitioned to universal recommendations. At this point, with a pandemic, we started out universal recommendation, but I'm not sure that we need to continue in that direction. And I wonder what your thoughts might be, or others around the table.

Dr. Monto: Well, just to go over ancient history, the reason we went over to universal recommendations, which were not universally agreed to by some well-known people, was the difficulty in interpreting risk groups. First we went to an age-based, down to age 50, and then we went to universal because it was very difficult to get the risks defined. I think, with COVID, we haven't really had enough time to see where to go. The factor of age seems to be much more important here, in terms of severe disease. And the question is also going to be what we're trying to prevent - whether we're trying to prevent all infections, or modest infections, which is one of the goals for influenza vaccination. So, I think we need to keep an open mind and watch the way things develop. Anybody else from CDC want to chime in about the recommendations? And then we'll go to break.

Dr. Levy: I would just add, Arnold, Ofer Levy here, that possibly preventing long COVID could be on the list too.

Dr. Monto: Yeah, there are a number of factors, and it's really early times to say which way things are going to be going. It is a little bit of a paradox right now. But, looking globally, saying the U.S. and Canada are among the few countries that have a universal recommendation, the same thing can be said for flu. Most countries don't have a universal recommendation, but that

hasn't affected the US in successfully having a universal flu recommendation. So, we're going to break now. We're going to return, I will say, in 10 minutes, which is going to be a little after 2:30 Eastern. Off to break.

**Committee Discussion of Vaccine Formula Selection and Voting**

Dr. Monto: And maybe, your summary.

Dr. Weir: Okay.

Dr. Monto: Just to refresh people's minds.

Dr. Weir: Okay.

Dr. Monto: And then open things up to questions, relative to the voting question, before we go ahead and vote.

Dr. Weir: Kathleen, can you bring the slides back up?

Ms. Hayes: Yes, AV team, can you pull up Dr. Weir's presentation, please?

Dr. Weir: Okay. Go to, toward the end. Okay, maybe now go back three. Yeah, that's good. So, this is where I was summarizing. I think I got through though.

Dr. Monto: Right.

Dr. Weir: This was a summary of both what I said, but also of everything that everyone had heard up until now. So by several measures, including increased escape from antibody neutralization and waning protection, the current COVID-19 vaccines appear to be less effective against currently circulating variants like JN.1. The manufacturers have told you that they've been evaluating updated candidate vaccines at risk. And they told you about their plans to provide updated vaccines for 2024 and 25. And as you've also heard, the manufacturing timelines may be impacted by the choice of the antigen. Next slide. And this was the other three points. To summarize non-clinical data, animal data from three different manufacturers indicated that updated monovalent JN.1 lineage formulations elicit stronger neutralizing responses against the

JN.1 descendant lineage viruses than current monovalent XBB 1.5 vaccines. The serology data from JN.1 infected individuals indicated improved neutralizing responses against JN.1 descendant lineage viruses, compared to sera from XBB infected individuals, but the neutralizing antibody responses appear to be reduced by recent amino acid mutations in these more recent JN.1 lineage viruses. But the totality of the available evidence indicates that a monovalent JN.1 lineage vaccine is warranted for COVID-19 vaccines 2024-2025 formula to be in the U.S. to more closely match the currently circulating SARS-CoV-2 viruses. And as I mentioned several times, the diversity of the JN.1 lineage viruses complicates the specific strain selection decision. So that was a summary. If you go forward now two slides, you see the voting question.

**Voting Question One**

Dr. Weir: Okay, so this was a voting question that the committee is being asked to decide on. For the 2024-2025 formula of COVID-19 vaccines in the U.S., does the committee recommend a monovalent JN.1-lineage vaccine composition? So that's the voting question. I don't know if you want me to go ahead and throw out the discussion topic that will come after this again. That's in the next slide.

Dr. Monto: No, I think it’s just critical here to reiterate that we're voting here on JN.1 lineage, which is not just JN.1.

Dr. Weir: That's true. And that mirrors what the TAG-COVAC recommended. So that was our starting point.

Dr. Monto: Okay, so now we can have some discussion about the voting question from the committee. Dr. Gellin.

Dr. Gellin: Yeah, I think it's pretty much, thanks a lot. It's similar to the question I asked at the top, is what counts as JN.1 lineage? Somebody, and maybe it was Dr. Thornburg, had a beautiful

dendrogram that showed the whole family of JN.1. So, if that's the question, then it's up to the manufacturers to pick whatever works best for them within that family?

Dr. Monto: I'll leave it to the FDA to answer that question.

Dr. Weir: Now, I think I may not have heard the last part. We're asking whether the committee agrees with the recommendation for a lineage vaccine composition. But then, following that, we will want your opinions about specific strains, and then the Agency will make a decision about whether the strain should be specific and what to recommend to the manufacturers.

Dr. Monto: Okay, thank you. So it's a two-stage action. First, we talk about the lineage, and then we opine about what that specific virus should be.

Dr. Weir: Exactly, yes.

Dr. Monto: Dr. Nelson.

Dr. Nelson: Just another quick clarifying question for Dr. Weir. I want to focus on the word A, in front of a monovalent JN.1 lineage vaccine composition. So the vote today is to open the door to a JN.1 lineage vaccine and not commit to a single one, having heard that we have differences between manufacturers with respect to their preparedness to field a vaccine by default.

Dr. Weir: Yes, that’s correct. I mean, that is the reason the discussion question is somewhat difficult. I think you've heard that all the manufacturers can probably meet the monovalent JN.1 lineage, but they have different levels of preparedness for some specific strains.

Dr. Nelson: Correct.

Dr. Monto: Okay, no hands raised. Okay, Dr. Wharton.

Dr. Wharton: Well, I'd like to thank all the speakers for really excellent presentations. And I think a pretty compelling case has been made that an updated vaccine's appropriate at this time,

and that a vaccine of the JN.1 lineage would be appropriate for an updated COVID vaccine for the 2024-2025 season.

Dr. Monto: Thank you. Looks like the case has been made. Oh, Dr. Meissner, okay. The committee is unusually silent.

Dr. Meissner: You waited too long. So, I felt I had to answer your question. I would say, first of all, we've all said that we don't want to start chasing variants, number one. Number two, we don't know much about the safety, in particular in terms of myocarditis, with these updated lineages, what that will be. Although there's no reason to think it would be any different a priori. And I think to follow up on the question that was just asked, we're not gonna have the option for a bivalent or multivalent vaccine at this stage. We're confined to this issue of a monovalent update. But I think that the data that have been presented this morning are pretty compelling. Thank you.

Dr. Monto: Thank you, Dr. Meissner. Are we ready to vote? Kathleen?

Ms. Hayes: Looks like it. Thank you, Dr. Monto. So for today, just as a reminder, we have eight voting members along with eight temporary voting members, so 16 in total who will be voting in today's meeting. You can see their names here. And with regards to the voting process, Dr. Monto, just for the record, I know this has been read a few times, but we'll have you read the voting question.

Dr. Monto: Okay, I'm almost ready.

Ms. Hayes: No, you're fine, you're fine. And then afterwards, all the voting members and temporary voting members will cast their vote by selecting yes, no, or abstain. Just as a reminder for everyone, you'll have one minute to cast your vote after the question is read. And then please note that once you've cast your vote, you can change your vote within the dedicated timeframe. However, once the poll has closed, all votes will be considered final. And once all the votes have

been placed, we will then broadcast the results and I will read the individual votes aloud for the record. So unless anybody has any specific questions regarding the voting process, we can have Dr. Monto read the voting question for the record.

Dr. Monto: Okay, and I'm ready now. For the 2024-2025 formula of COVID-19 vaccines in the U.S., does the committee recommend a monovalent JN.1-lineage vaccine composition? Yes, no, or abstain.

Ms. Hayes: Thank you. And then at this point, if our AV team can go ahead and move all non-voting members out of the main room. To non-voting members, please don't log out of Zoom. Just note that it will be silent for anywhere between two to five minutes. So just don't be alarmed by that. And we will be back within a few minutes once the vote is complete. Okay, and if we could get the Excel sheet displayed, I will read aloud the votes. Thank you. Okay, so out of the 16 total voting members for today's meeting, we have 16 yes votes and zero no votes. So, I'm just going to read the individual voting responses for the public record. Captain Sarah Meyer, yes. Dr. Ofer Levy, yes. Dr. Randy Hawkins, yes. Dr. Mark Sawyer, yes. Dr. Adam Berger, yes. Dr. Bruce Gellin, yes. Dr. Paul Offit, yes. Dr. Arnold Monto, yes. Dr. Jeanette Lee, yes. Dr. Archana Chatterjee, yes. Dr. Stanley Perlman, yes. Dr. Melinda Wharton, yes. Dr. Michael Nelson, yes. Dr. Cody Meissner, yes. Dr. Henry Bernstein, yes. And Dr. Haley Gans, yes. So this concludes the voting portion for today's meeting. And I will now hand it back over to the chair, Dr. Monto, for any voting explanations needed and to move forward into the discussion topic. Thank you.

Dr. Monto: First, anybody wish to explain their vote before we go on to the discussion about which of the JN.1 lineage we think ought to be in the monovalent vaccine? Seeing no hands raised, let's move on to the discussion. I think you've already heard the summary from Dr. Weir. And the fact that this is going to be a monovalent vaccine. So, what we have there is the

discussion topic. Based on the evidence presented, please discuss considerations for the selection of a specific JN.1 lineage strain, JN.1, KP2, et cetera. So it's KP3, I guess, for COVID-19 vaccines, the 2024-2025 formula to be used in the U.S. Okay, Dr. Chatterjee.

Dr. Chatterjee: Thank you, Dr. Monto. From my review of the data, it appeared that the newer variants that are appearing, KP2, KP3, and maybe some others that are coming up, the potential for immunogenicity from a JN.1 vaccine to cover those variants seems to be pretty good. Antigenically, they are close. And from the experience we've had with XBB, it appears even with some variation, there's still reasonably good protection. So, from that perspective, I would say that a JN.1 is a reasonable strain to include. As some people have said already today, the WHO has talked about it, that we're not going to be trying to chase variants. And whatever we choose today or recommend today is probably not what is going to be circulating a few weeks or a few months from now. As long as there is sufficient cross protection anticipated, I think it's reasonable to select JN.1.

Dr. Monto: Thank you. Dr. Sawyer.

Dr. Sawyer: Yeah, I agree. And I think unless we have compelling reason to do otherwise, given the limitations of Novavax, I think we do need to just recommend a JN.1 version. Otherwise, there are going to be equity issues or access issues to those who are reluctant to get mRNA vaccines. So, I did not hear a compelling reason to favor a different strain. So I'm in favor of JN.1.

Dr. Monto: Dr. Berger.

Dr. Berger: I'll say I also agree. I think the antigenic close relationship between JN.1 and its sub-lineages, and the cross-reactivity we saw in the presented data across KP2 and KP3, really does suggest that JN.1 is the appropriate vaccine update to be making at this time. And just as Dr.

Sawyer was mentioning, it does also ensure that there's both an mRNA and a protein-based vaccine option available to the public. However, I do want to make one note about this, because I do think this is a limitation here. And I'm concerned that it could end up putting us at a position in the future where, depending on what the protein vaccine can be made from, or made out of, that that will require us to go down this path. I'd like to make sure we don't get in that position in the future. I'm not saying we're in that right now, but I do want to make sure we have all options on the table, should a different variation be required in the future. As I said, right now, I think JN.1 is the right call. So that doesn't seem to be an issue, but I just want to point that out, that that could present some type of problem for us at some point. Thank you.

Dr. Monto: Thank you. Dr. Wharton.

Dr. Wharton: Thank you. I agree with the comments previously made. I think we can't predict which variants are going to emerge over the coming months. It may very well not be any of the ones that we're talking about today, but they're likely to be related to JN.1. So having a vaccine that's the trunk of the tree rather than the branches makes sense to me. I think the chances of having broad cross protection are probably greater, and I am concerned about not potentially having all the vaccine platforms available, should a different strain be recommended. So I'd be supportive of JN.1.

Dr. Monto: Dr. Perlman.

Dr. Perlman: Yeah, I agree with what's been said so far. I just want to add one point, which is that in the beginning of the pandemic, it was pretty clear the neutralizing antibodies were a great correlate of protection, and now it's a little less clear. It's certainly important. So, even if we didn't have the Novavax constraint, I would probably not have a strong opinion about which way

to go, because I don't think we know, and we don't even know what the most effective way to prevent the next rounds of the pandemic are, even in the outside of all these other questions.

Dr. Monto: Thank you, Dr. Perlman. Dr. Marks, would you like to give us some guidance?

Dr. Marks: Yeah, I'm just a little concerned that perhaps the committee doesn't understand that if they choose to recommend, or to make any comments about a KP2 vaccine, that does not mean that there will not be availability of a JN.1 Novavax vaccine necessarily. It just may mean that there will be two different formulations available. Now, you might say, how could that be? But that's precisely what happened two years ago, when Novavax had their original vaccine available, when we had a bivalent available. And yes, there was some preference given towards an updated vaccine. I guess we could consider how we would word this, now. But I would ask for the committee to comment a little bit on this concept. We're saying we will settle for a JN.1, but I'd just kind of like to understand from a scientific standpoint, do we think there's some possibility that KP2 and KP3 are potentially going to evolve back closer to JN.1? Because all of the data seem to show that neutralization, granted, we're not saying that that's a big deal here, except perhaps in newly vaccinated individuals, if you look closely at that. Do we really think that we're, I mean, are we really okay with this? And if this evolves further in the fall, will we regret not having been a little bit closer? I guess the point here being that, yes, we shouldn't be chasing, we always say we shouldn't be chasing strains, but we're paying an incredibly high premium for mRNA vaccines to be able to have the freshest vaccines. The analogy that I would make here is that, at least for me, when I go to the milk case to buy milk, despite the fact that all the milk I buy is ultra pasteurized, and it's never going to go bad before I use it, I always tend to buy the most recent dating rather than an older dating. And that's just in case. So the question, I just would love the committee to comment a little bit more about this, knowing that so well, that

we might have a solution for the Novavax issue. That our intention is not to take away choice, but it's to just accept that this is the nature of mRNA versus protein-based vaccines. Over.

Dr. Monto: Dr. Marks, does that mean we're going again the way of flu vaccine, where the recommendation is for something like, and the manufacturers have a choice within a prescribed number of strains to produce the vaccine that they wish to?

Dr. Marks: I suspect that we can talk about this. I would ask Jerry and Dr. Castle to comment, but I think we would be saying that a JN.1 vaccine could be acceptable in this scenario, particularly given what everyone on the committee has already said. I think the question is, there would be a choice then that people would make with, you've said basically that you think they're basically equivalent. For those who feel more comfortable with a protein-based vaccine, they would maybe say that, well, a JN.1 protein-based vaccine is perfectly fine for me. Some people might say, including some people who I think were at the open public hearing, might say, look, we want the thing that's most likely to be closest to what will be circulating. Again, I'd love the committee to comment on whether we think that the head of this thing is going to go and change so that it's more like a JN.1 ever again, rather than something different than a KP2 or three. And so, I think there are ways to deal with this. And that may be one of them, to give manufacturers the options.

Dr. Monto: Yeah, I think one of the things that may be troubling a single choice is the schematic which showed JN.1 in the middle and KP2 in one direction, and KP3 in the other direction. So, it becomes a little bit of a problem trying to come up with a unitary choice. Does anybody else from the FDA wish to comment at this point?

Dr. Weir: Yeah, Dr. Monto, this is Jerry. I just want to make one comment about your question about going in the like way, something ‘like’. In influenza, that terminology is well-defined, and

people understand what it means to be something ‘like’ virus. Unfortunately, we're not there yet with SARS-CoV-2. We don't know whether two-fold, four-fold, eight-fold is still ‘like’ or not. So I just caution you that we had years to develop that terminology for influenza and I don't think we're there yet with SARS-CoV-2. Over.

Dr. Monto: No, I'm not proposing that. I'm just proposing having the ability to have different specific variants in the vaccine. And we may be there with COVID in another couple of years, but I agree, we're not there yet.

Dr. Weir: Yeah, and I agree. I just don't think everyone can define it themselves.

Dr. Monto: Right.

Dr. Weir: Okay. Over.

Dr. Monto: But what I'm saying is a non-unitary choice. Okay, Dr. Meyer.

Dr. Meyer: Yes, so I also think a JN.1 vaccine would be most appropriate for this season to try to address some of the points that Dr. Marks brought up. From my perspective, I think it's just really hard to predict what is going to happen and where things are going to go. So, I do see kind of reason with the thinking that JN.1 is further up on the tree. And so, if we had to guess, or we had to choose, that seems to be an appropriate option. But I personally wouldn't be able to make those kinds of guesses of where we think this could be going. I think we've all seen how much evolution has occurred, and how much change has occurred over the years. But I did want to comment a little bit on the Novavax, and I guess also to add to that, the data that we did see for JN.1 and KP2, I agree with the other committee members that either looks to be sufficient. But I did want to comment on one issue that I'm not very sure that that was cleared to the entire committee, that there was a possibility of JN.1 and KP2 vaccines. One of my comments was going to be, I think it is important to have Novavax as an option this season for people who

cannot or do not want to take an mRNA vaccine. So, I do think some additional confirmation and clarity there is helpful. The final important quick point I want to make is that I think we've heard from the manufacturers that they all said they would be prepared for either vaccine choice, but I do think that timing is really important. Having the vaccine at the beginning of the season, in case there's an early surge or so that we can have, you know, options for co-administration with flu vaccine, and just overall better planning preparedness is very important. So while I thought it was reassuring that manufacturers stated they would all be ready regardless of the vaccine choice, I mean, the planning has already kind of started, presuming JN.1. So, I think that seems to be an option that would facilitate implementation as well. And I'll pause there.

Dr. Monto: Thank you. Dr. Gans.

Dr. Gans: Thank you. I wanted to agree with my colleagues that I think JN.1, despite the fact that what we're seeing is some reduced antigenicity against the more divergent strains, KP3, if you really look at the data, and since we don't have exact tighter correlation for protection, I think if it goes in a different direction, having a JN.1 would allow for some protection in a different direction as well. So, while the KP3 is maybe emerging at this time, given that we can't predict where it's going. I think that would diversify our immune response enough and then perhaps catch some, if there was further strain replacement in a different direction. So, I do think that that's probably the right decision at this point. I would just add, and for all the reasons that my colleagues have discussed, I would want to just reiterate that it would be lovely to have this conversation earlier, so that we would have some different data choices. So again, we are are being asked about a monovalent, like our flu vaccine, and the ways that we're going with that, is it possible to have a bivalent if we did see any kind of more divergence? So I think those questions really need to come before us as we're considering vaccines in the future. I think that

for right now and the decision for this year, the JN.1 actually looks like the right choice. In terms of something that I wanted to bring up since we didn't get back to it, I have a lot of faith in our surveillance systems in the safety data. So I want to dispel any of wanting that information. My request was not because I had concerns, but I think in terms of the discussions that have been brought up in terms of public trust, we're trusting in our vaccines, is that that data needs to be presented in the public record, and that's why I was trying to push our colleagues to give us some of that data. I do think it should come before us when we're being asked to look at vaccines. I think the data profiles, as they've outlined, have been very good, but there's also been some additional entities that should be looked at again. Also, what was brought up for long covid, there have been some data to suggest that they're actually protective or helpful in that direction. So I think there's a lot of societal concerns that could be alleviated or at least discussed in this forum. And I just wanted to put the plug in for where we're going. Thanks.

Dr. Monto: Thank you. And I agree. The problem is that we really need to have a session directed towards that, because there are other under surveillance systems that we would want to hear from. Dr. Levy.

Dr. Levy: Thank you. The selection of JN.1 would make sense, so I agree with the other committee members regarding their comments on that. I do want to put a plug that we need to keep getting better. We've heard throughout the day, our desire to be better at projecting which variants will emerge and take over, that we need to get better at defining relationships between anybody titers and vaccine efficacy. That we need to get better at understanding correlates of protection, including age-specific correlates of protection. And in regard to all these important aspects that we need to get better at, I would highlight to the public that on the 29th of December, 2022, the president of the United States signed the FDA Modernization Act 2.0,

which provides for additional paths to generate data and support of FDA filings, including human in vitro modeling and the use of artificial intelligence. And I'm really hoping that FDA and the sponsors are investing in these areas, so that we keep getting better. Because we're going to raise these same questions and limitations again and again. Thank you.

Dr. Monto: Thank you. Dr. Gellin.

Dr. Gellin: Thanks. Yeah, so as much as we want to have this fit into our influenza model, it really doesn't. And we keep talking about that season, the seasonality. I've been struck, anecdotally, by the number of people that I know who had COVID in the last month, and the overlay is that people are inside more, because they're inside with air conditioning, which is sort of the winter story of people are inside because it's cold outside. So, we have to try to break from that model, which gets back into what the right cadence is for these kinds of decisions. This meeting was originally scheduled in mid-May. I don't know exactly why it was delayed. My guess was to see what the variance is and see where we were. Dave Wentworth told us about what the timing was when the WHO made its decision, and we don't have a crystal ball. But I think there's been a sufficient argument if we're going to stick with a monovalent for now, that as Melinda said, the trunk of the tree probably is our best bet for now. The surveillance will keep an eye on things, but then the question is, when should we look at this again? The framing is that this is a formula for 2024 to 2025, which also implies a year, and suggests that that may not be it. So, I think I'm okay with the trunk of the tree on this one, but we need to think through how we can maybe come closer to the end, and now that we know how Peter buys milk.

Dr. Monto: Dr. Chatterjee.

Dr. Chatterjee: Thank you, Dr. Monto. So, I'm glad Dr. Marks brought up the question because that was a question actually that I had thought about myself, and kind of answered for myself, to

say, you know, we have different formulations of many vaccines. Not necessarily the flu or other respiratory viral vaccines, but we do for pneumococcal, meningococcal, there are many different formulations. So, there's no reason to suppose that we couldn't have a different formulation or a number of different formulations for this vaccine. Having said that, I do think about some potential for confusion, particularly there were different variants included in different vaccines. There's enough confusion already about this vaccine, and particularly for the public, but also perhaps for providers, if there were different formulations then that might create some problems with implementation and administration of the vaccines.

Dr. Monto: Thank you. Dr. Sawyer.

Dr. Sawyer: Thank you. Yeah, I want to follow up on Dr. Chatterjee's comment just then, and to the question of whether we should allow the manufacturers to choose what strains go into it. I think at this point, that would be a mistake, because of the confusion that it will create. Given the lack of hard data about how the public or individual providers would then decide whether to give a vaccine or not. As I understood the comment from Novavax, if a KP2 strain was selected, they would not necessarily deliver vaccine on time. And I think that, at this point, is a major problem in the delivery of vaccine. It needs to be equitably available to everybody at the same time. So, I think, given all the uncertainties, the safest thing is just to JN.1.

Dr. Monto: Dr. Nelson.

Dr. Nelson: Thank you, Dr. Monto. First, for the record, I want to applaud the systematic approach taken by the FDA manufacturers and CDC to address this challenge, as posed by this ever-evolving SARS-CoV-2 virus. It's been a heroic effort, and everyone should take some comfort in the way it's been managed to date. I think you'll gain from the genesis of the question I asked about the voting question, was the issue of whether or not there could be multiple

vaccines available. And I appreciate the comments of Dr. Marks for opening that door. So I will tell you that my preference, with a clean slate and no constraints, including a monovalent vaccine, would be to have a polyvalent vaccine that had both JN.1 and KP2. Understanding the constraints and the issues before us today, my individual preference would be for a KP2 vaccine, based on the immunologic response data that's been presented, as well as a public thirst for the latest and greatest, without introducing any known risk from that selection. However, for reasons that have been articulated by my colleagues, I want the committee to know that I'm very fully supportive of the choice of JN.1 as a single vaccine, because I too think that having early access, the simplicity of a single strain for the public consumption, at this time of the evolution of the vaccine, and the comfort from the neutralization data presented, that JN.1 is a natural and obvious choice going forward. Thank you.

Dr. Monto: Thank you. Dr. Meissner.

Dr. Meissner: Thank you, Dr. Monto. I'd like to make one comment that may not be so helpful for the discussion today, but hopefully may be helpful for discussions in the future. And that is to remind everyone that the Department of Health and Human Services has committed $5 billion to develop medical countermeasures, including improved COVID vaccines. And through BARDA, there are a number of new vaccine platforms that will be supported, that will start in the next 12 months or so. And part of the high interest areas include the role of cellular immunity because that's come up several times today, that address the issue of neutralizing antibodies, what's critical, and what isn't. And so hopefully in time, we're going to have some solid data to begin to address these questions. Over.

Dr. Monto: Thank you. Just as a general comment, the last time we had a discussion like this about COVID vaccines, we were faced with a couple of different lineages that were quite

different one from another. The advantage we have now is that we're really talking about two specific viruses, which are within the same lineage. So, the importance is a little minimized in terms of what we choose. The serologic data show a whole lot of overlap. Unlike the situation before, we've heard very little about the stability of the spike and other considerations that if we had more time, would be part of the equation. Dr. Marks, what would you like to hear from us in terms of further discussion? We've actually again exhausted the list of those who have their hands raised.

Dr. Marks: No, I think it's clear. People feel like, despite the fact that I think we saw data that suggested that, just for the record, data was presented, and I'd ask the manufacturers to chime in. I believe even Novavax provided data that showed that it does seem like JN.1, we've seen the data very clearly, JN.1 seems to adequately neutralize here. I think there might be some data that was presented that suggested that a KP2 vaccine could neutralize both JN.1 and KP3. But accepting that, I think the idea of getting a vaccine a week or two sooner is very attractive to the committee. We understand that. I think the concept of having Novavax available, which by the way, it would be helpful if we could probably next time, we'll show you the percentage of Americans who received these different vaccines but represents a small fraction of the vaccine administered. I think the committee should be aware of that, next time. So we'll make sure we present those data next time. So you know where the distribution here is, because at the end of the day, 95% plus of the vaccine that was administered last year was mRNA vaccine. And a large part of the reason for the mRNA vaccines has been this ability to update them. And that was the reason why we delayed this VRBPAC meeting until now, to see in case the committee wanted to update it. I think we hear loud and clear that you're happy with the JN.1. And so, we hear that's the recommendation of the committee and really appreciate the discussion here. And this actually

will keep us all, if we do decide to go with the JN.1 as the recommendation, the committee feels like it should be for all of the manufacturers and there should not be an option. So I think unless anyone doesn't think I've summarized their feelings here, I think we probably are almost done with our work.

Dr. Monto: Dr. Nelson has his hands raised.

Dr. Nelson: Yes, you summarized my feelings.

Dr. Monto: Don't go away, Dr. Marks. I want to get back to the issue of safety.

Dr. Nelson: Yes, and I've tried to focus my remarks to date on the matter at hand with strain selection, but I did want to make a few comments in general, as some of my colleagues have done throughout the day. I do echo the concern for us developing a strategic roadmap that is really dedicated to identifying correlates of protection that represent both humoral and cellular immune responses. But there was also today a striking absence of gender, race, ethnicity, safety, and efficacy data. So, my assumption is that there was adequate inclusion as part of these studies, but it would be very reassuring to hear data from the manufacturers, and from the literature review, that supports that there is some equity along those lines. And then finally, we heard throughout the public comment period, several individuals confused by the term immunocompromised. So, my plea to the CDC and FDA is that we liberalize that definition, and not introduce constraints for individuals truly motivated to receive multiple vaccines throughout the day, and allow some form of self-declaration along with their physicians that enables them to get those vaccines, and to get the adequate insurance coverage that is needed by some of those individuals. Thank you.

Dr. Monto: Dr. Marks, do you have any comments? The issue of safety was raised. I said that to really have a thorough discussion of safety, we really need other participants to be involved.

Dr. Marks: Yeah, I think I hear loud and clear. And so I think I can go back. Dr. Kaslow is on as well. We can go back and make sure that next time we have both CDC and FDA's folks on, so that they can present the safety data. But there were, as noted, you don't have to take my word for it, but there were no new safety concerns with this year's vaccines.

Dr. Monto: Right, we're dealing with vaccines that are so safe, you have to have reasonably high numbers to find any of the signals, correct?

Dr. Marks: Well, I mean, there are a few signals that we can detect, right? We can detect some anaphylactic reactions and myocarditis, but even those are pretty uncommon. And these are pretty safe vaccines.

Dr. Monto: Dr. Gans.

Dr. Gans: I do follow the surveillance data. So again, the reason that I'm bringing it up is not because I'm concerned, but I do think that there has to be an effort to present the data, even if there's quote no new findings, that in itself would be something that I think would be important to include. Additionally, I feel that it would also be very important for the public record to understand exactly what is being considered through the surveillance system, so that people understand if there's a new signal, how that would be evaluated, and because we understand that the ones that have already been highlighted are no more frequent than they had been in the past. And again, all that is reassuring. I just feel like when we have these discussions, like we do annually for flu, I'm not saying this is the same disease. So, I think that that's not why we keep bringing up influenza, but the frequency of our meetings at this point appears to be so. So that's the reason we raise it.

Dr. Marks: Understood.

## Closing Remarks

Dr. Monto: Okay, so I'm going to pass the meeting over to Dr. Marks for some closing remarks, and then he can go to our designated federal officer to close the meeting.

Dr. Marks: So, first of all, thank you, Dr. Monto, very much. And thanks to all the members. Really appreciate the feedback today. It actually was very helpful. This was a good check. We wanted to make sure that we gave people the option to potentially make a choice of a KP2 vaccine. We hear loud and clear from all of the members that they don't feel like that is necessary at this time, that a JN.1 vaccine for all is acceptable. We take that back. We really appreciate your feedback in that regard. And we hear the other suggestions for the future, perhaps for some more frequent updates, as well as for safety information. And with that, I just want to say thank you so much to all of the members of the committee. Thank you, Dr. Monto. I also want to thank the advisory committee staff, the staff that has helped broadcast this meeting, and all of our Office of Vaccines, our Office of Biostatistics and Pharmacovigilance, who have helped put together this meeting. Very much appreciate it. And really, we'll look forward to future meetings moving forward. So I will turn it back over to either you, Dr. Monto, or to our designated federal official.

Dr. Monto: Let’s go over to Kathleen.

## Adjournment

Ms. Hayes: Great. Thank you, everyone. Just echoing, appreciate the time today. It is currently 3:26 Eastern Standard Time. And this meeting is now adjourned. Thank you.

# Table of Contents