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Center for Biologics Evaluation and Research (CBER)
175th Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting

OPEN SESSION

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

ATTENDEES

COMMITTEE MEMBERS	
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Henry Bernstein, D.O., MHCM, FAAP	Zucker School of Medicine at Hofstra/Northwell Health
Archana Chatterjee, M.D., Ph.D.	Rosalind Franklin University
CAPT Amanda Cohn, M.D.	National Center for Immunizations and Respiratory Diseases Centers for Disease Control and Prevention
CAPT David Kim, M.D.	U.S. Department of Health and Human Services
Arnold Monto, M.D.	University of Michigan
Paul Offit, M.D.	The Children's Hospital of Philadelphia
Steven A. Pergam, M.D., M.P.H., FIDSA	Seattle Cancer Care Alliance
Gregg Sylvester, M.D., M.P.H.	Seqirus Inc.
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Randy Hawkins, M.D.	Charles Drew University and Private Practice
James Hildreth, Sr., Ph.D., M.D.	Meharry Medical College
Jeannette Lee, Ph.D.	University of Arkansas for Medical Sciences
Ofer Levy, M.D., Ph.D.	Massachusetts Institute of Technology
Wayne A. Marasco, M.D., Ph.D.	Harvard Medical School
Cody Meissner, M.D.	Tufts University School of Medicine
Michael Nelson, M.D., Ph.D.	UVA Health & UVA School of Medicine
Stanley Perlman, M.D., Ph.D.	University of Iowa

Arthur Reingold, M.D.	University of California, Berkeley
Mark Sawyer, M.D., F.A.A.P.	Rady Children's Hospital San Diego
Melinda Wharton, M.D, M.P.H.	Centers for Disease Control and Prevention
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Matthew Biggerstaff, Ph.D.	Centers for Disease Control and Prevention
Gregory Glenn, M.D.	Novavax
Stephen Hoge, M.D.	Moderna Therapeutics
Justin Lessler, Ph.D.	University of North Carolina
Ruth Link-Gelles, Ph.D.	Centers for Disease Control and Prevention
Heather Scobie, Ph.D., M.PH.	Centers for Disease Control and Prevention
Kanta Subbarao, M.D. M.PH.	University of Melbourne
Kena Swanson, Ph.D.	Pfizer, Inc.
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Catharine Diehl, PhD	
Kate Schenk	
Aime Baker	
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Valerie Burek	Stand for Health Freedom
Hershie Klein, MD	

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OPENING REMARKS: CALL TO ORDER AND WELCOME

MR. MICHAEL KAWCZYNSKI: Good morning and welcome to the 175th meeting of the Vaccines and Related Biological Products Advisory Committee Meeting. I'm Michael Kawczynski, and I along with my colleagues here at FDA will be running and managing today's meeting. This is a 100 percent live virtual meeting. We have members and participants from around the world joining us today. So please note with any live meeting, if we do have any technical glitches, which can occur, we'll take a momentary pause, get those fixed because we don't want you, the consumer, and all that to miss any of the content in today's meeting.

So that being said, I am going to hand it off to our chair, Dr. Arnold Monto. Dr. Monto, are you ready?

DR. ARNOLD MONTO: I am. I'd like to welcome everybody --

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

DR. ARNOLD MONTO: Okay. I'd like to welcome everybody to the 175th meeting of the Vaccines and Related Biologics Products Advisory Committee of the FDA. Our topic for the day, which is a critical one, the Committee will meet in open session to discuss whether and how the SARS-CoV-2 strain composition of the COVID-19 vaccines should be modified. Now I'd like to turn the floor over to our Designated Federal Officer, Prabha Atreya, who will handle the introductions and the housekeeping issues. Prabha.

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

DR. PRABHAKARA ATREYA: Thank you, Dr. Monto. Good morning, everyone. This is Dr. Prabha Atreya, and it is my privilege and great honor to serve as the Designated Federal Officer, that is DFO, for today's 175th Vaccines and Related Biological Products Advisory Committee. On behalf of the FDA, the Center for Biologics Evaluation and Research, and the VRBPAC Committee, I'm happy to welcome everyone for today's

virtual meeting.

Today the Committee will meet in open session to discuss whether and how the SARS-CoV-2 strain composition of COVID vaccine should be modified. Today's meeting and the topic were announced in the federal register notice that was published on March 31, 2022. At this time, I would like to introduce and acknowledge the excellent contributions of the staff and the great team we have in my division in preparation for today's meeting.

Ms. Christina Vert is my backup DFO, who has been assisting with many meeting preparations. Dr. Sussan Paydar is my alternate DFO, who will read the conflicts of interest statement for the public record and also who will be conducting the voting process later today. In addition to Sussan and Christina, other staff who contributed significantly are, Ms. Joanne Lipkind, Ms. Karen Thomas, and Lisa Wheeler and Viola Sampson who have also provided excellent administrative support.

I would also like to express our sincere appreciation to Mike Kawczynski in facilitating this

meeting today. Also, our sincere gratitude goes to so many CBER and FDA staff working very hard behind the scenes trying to ensure that today's meeting -- virtual meeting -- will also be a successful one like all the previous Vaccines Advisory Committee meetings recently. Please direct press and media questions for today's meeting to FDA's Office of Media website fdaoma@fda.hhs.gov. The transcriptionist for today's meeting is Ms. Ora Giles.

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

DR. ARNOLD MONTO: Yes. Thank you, Prabha. Good morning, again, to everybody. I'm Arnold Monto. I'm at the University of Michigan School of Public Health where I have been working for many years on

influenza and other respiratory viruses, including the coronaviruses. And I have been -- just as background, I have been involved in one respect or another for many years in influenza strain selection handled by WHO and FDA. Thank you.

DR. PRABHAKARA ATREYA: Thank you, Dr. Monto. Next, Dr. Hayley Gans.

DR. HAYLEY ALTMAN-GANS: Good morning, everyone. This is Dr. Hayley Gans. I am a pediatric infectious disease physician at Stanford University, and my research focus is on the immune response to vaccines. And I also sit on regulatory bodies to assess safety of vaccines.

DR. PRABHAKARA ATREYA: Thank you, Dr. Gans. Next is Dr. Berger. Adam Berger.

DR. ADAM BERGER: Hi, I'm Adam Berger. I'm a geneticist by training. I'm the director of the division of clinical and healthcare research policy at NIH where I oversee all of our clinical research in clinical trial policies. Thanks

DR. PRABHAKARA ATREYA: Thank you. Next, Dr. Hank Bernstein.

DR. HENRY BERNSTEIN: Good morning, everyone. I'm Hank Bernstein. I'm a professor of pediatrics at Zucker School of Medicine at Hofstra/Northwell. I'm a general pediatrician with expertise in pediatrics and vaccine.

DR. PRABHAKARA ATREYA: Thank you. Next is Dr. Archana Chatterjee.

DR. ARCHANA CHATTERJEE: Good morning. My name is Archana Chatterjee. I serve as the dean of Chicago Medical School and vice president for medical affairs at Rosalind Franklin University of Medicine and Science. I am a pediatric infectious diseases specialist, and my area of focus within pediatric infectious diseases is in the field of vaccinology. Thank you.

DR. PRABHAKARA ATREYA: Thank you. Next, Dr. Amanda Cohn.

CAPT. AMANDA COHN: Good morning -- excuse me. I'm Dr. Amanda Cohn. I'm a pediatrician at the Centers for Disease Control and Prevention. Of there, I have had experience in vaccine policy and maternal and child health.

DR. PRABHAKARA ATREYA: Thank you. Next is Captain David Kim.

CAPT. DAVID KIM: Good morning. This is David Kim with the National Vaccine Program in the HHS, Office of the Assistant Secretary for Health.

DR. PRABHAKARA ATREYA: Thank you. Next is Dr. Paul Offit.

DR. PAUL OFFIT: Good morning. I'm Paul Offit. I'm an attending physician in the division of infectious diseases at the Children's Hospital of Philadelphia, a professor of pediatrics at the University of Pennsylvania School of Medicine, and my published area of research interest is in mucosal vaccines. Thank you.

DR. PRABHAKARA ATREYA: Thank you, Dr. Offit. The next one is Dr. Steven Pergam.

DR. STEVEN PERGAM: Thanks, Prabha. I'm Steve Pergam. I'm an adult infectious disease physician at the Vaccine and Infectious Disease Division at Fred Hutchison Cancer Research Center, and my focus is infections and immunocompromised health.

DR. PRABHAKARA ATREYA: Thank you. Next is

Dr. Greg Sylvester.

DR. GREGORY SYLVESTER: Good morning, my name is Greg Sylvester. I'm the pediatrician and preventive medicine physician, and I'm the alternative industry representative. I work with Seqirus Vaccines.

DR. PRABHAKARA ATREYA: Thank you. Next, I'm going to introduce our temporary voting members starting with Dr. Oveta Fuller. Unfortunately, she will not be able to attend the meeting today due to a medical issue. And then so we're going to moving forward to Dr. Bruce Gellin.

DR. BRUCE GELLIN: Thank you. Good morning, I'm Dr. Bruce Gellin. I'm currently the chief of global public health strategies at the Rockefeller Foundation. I trained in adult infectious diseases and had a past life, where David is now, at the Department of Health and Human Services, directed the National Vaccine Program Office for 15 years, and, like Arnold, have been on many of these committees where we were doing influenza strain selection. Thanks.

DR. PRABHAKARA ATREYA: Thank you, Dr. Gellin. Randy Hawkins is the alternate consumer rep.

DR. RANDY HAWKINS: Randy Hawkins, internal medicine, pulmonary and critical medicine private practice, Charles Drew University in Los Angeles, California.

DR. PRABHAKARA ATREYA: Thank you. Next is Dr. Jeannette Lee. Sorry, James Hildreth.

DR. JAMES HILDRETH: Good morning. Thank you, Prabha. I'm James Hildreth. I'm the president and CEO of Mary Medical College, professor of internal medicine, and I'm an immunologist and I study viral pathogenesis. Thank you.

DR. PRABHAKARA ATREYA: Thank you, Dr. Hildreth. Next is Dr. Jeannette Lee.

DR. JEANNETTE LEE: Yes, good morning. I'm Jeannette Lee. I'm a professor of biostatistics and a member of the Windsor P. Rockefeller Cancer Institute at the University of Arkansas for Medical Sciences. Thank you.

DR. PRABHAKARA ATREYA: Thank you. Next is Dr. Ofer Levy.

DR. OFER LEVY: Hi, good morning. My name is Ofer Levy. I am an attending physician in pediatric

infectious diseases at Boston Children's Hospital, professor of pediatrics at Harvard Medical School, and I direct the Precision Vaccines Program which is a multi-disciplinary group advancing next generation vaccines by applying precision medicine principles to vaccinology. Thank you.

DR. PRABHAKARA ATREYA: Thank you, Dr. Levy. Next is Dr. Wayne Marasco.

DR. WAYNE MARASCO: Good morning. I'm Wayne Marasco. I'm a professor of medicine at Dana-Farber Cancer Institute at Harvard Medical School. I'm an adult infectious disease physician, and I study host interactions, virus evolution, and immune adaptation. Thank you.

DR. PRABHAKARA ATREYA: Thank you. Next is Dr. Cody Meissner.

DR. CODY MEISSNER: Thank you, Prabha. Good morning to everyone. My name's Cody Meissner. I'm a professor of pediatrics specializing in infectious disease and vaccinology at Tufts University School of Medicine. And because Tufts Children's Hospital will close in the next few weeks, I will soon have another

academic address. But I appreciate the opportunity to participate today. Thank you.

DR. PRABHAKARA ATREYA: Thank you, Dr. Meissner. Next is Dr. Michael Nelson.

DR. MICHAEL NELSON: Good morning, Dr. Atreya. Thank you. I'm Mike Nelson. I'm professor of medicine and chief of the division of asthma, allergy and immunology at the University of Virginia. I'm also the president of the American Board of Allergy and Immunology. I'm a trained allergist and clinical immunologist with special interest in vaccine immune response and rare adverse events. Thank you very much.

DR. PRABHAKARA ATREYA: Thank You, Dr. Nelson. Next is Dr. Stanley Perlman.

DR. STANLEY PERLMAN: Good morning, Prabha. I'm a professor of microbiology and immunology and a pediatric infectious diseases specialist at the University of Iowa. I have been studying coronaviruses for 40 years now.

DR. PRABHAKARA ATREYA: Thank you. Next is Dr. Art Reingold.

DR. ARTHUR REINGOLD: Good morning, Prabha.

Art Reingold. I'm an infectious disease epidemiologist with the University of California School of Public Health, Berkeley. Thank you.

DR. PRABHAKARA ATREYA: Thank you, Dr. Reingold. Next is Dr. Mark Sawyer.

DR. MARK SAWYER: Good morning. Mark Sawyer. I'm a professor of pediatric infectious disease at University of California, San Diego, and Rady Children's Hospital in San Diego. And my area of focus is in the public health delivery of vaccines.

DR. PRABHAKARA ATREYA: Thank you so much, Dr. Mark Sawyer. Last but not least, Dr. Melinda Wharton.

DR. MELINDA WHARTON: Good morning. I'm Melinda Wharton. I'm an adult infectious disease physician by training and have been at CDC's immunization program for many years where I currently work in vaccine policy.

DR. PRABHAKARA ATREYA: Thank you, Dr. Wharton. And as you can see, we have a lot of experts set on the table. We have a total of 22 participants: 21 voting and 1 non-voting member. Now I will call upon Dr. Sussan Paydar to read the conflicts of

interest statement for the public record. Sussan.

DR. SUSSAN PAYDAR: Good morning, everyone. My name is Sussan Paydar. It is my honor and pleasure to serve as the alternate Designated Federal Officer for today's VRBPAC meeting. Thank you for your attention as I proceed with reading the FDA conflict of interest disclosure statement for the public record.

The Food and Drug Administration, FDA, is convening virtually today, June 28th, 2022, the 175th meeting of the Vaccines and Related Biological Products Advisory Committee, VRBPAC, under the authority of the Federal Advisory Committee Act, FACA, of 1972. Dr. Arnold Monto is serving as the acting voting chair for today's meeting. Today, on June 28th, 2022, under topic one, the Committee will meet in open session to discuss whether and how the SARS-CoV-2 strain composition of COVID-19 vaccine should be modified. This topic is determined to be a particular matter involving specific parties, PMI-SP.

With the exception of industry representative member, all standing and temporary voting members of the VRBPAC are appointed special government employees,

SGEs, or regular government employees, RGEs, from other agencies and are subject to federal conflicts of interest law 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 at this meeting, all members, RGE and SGE consultants, of this Committee, have been screened for potential financial conflicts of interest of their own, as well as those imputed to them including those of their spouse or minor children, and for the purposes of 18 U.S. Code 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts and grants, office of research and development agreement, teaching, speaking, writing, patents and royalties, and primary employment. These may include interests that are current or under negotiation. FDA has determined that all members of this advisory committee, both regular and temporary

members, are in compliance with federal ethics and conflicts of interest law.

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 conflicts of interest when it is determined that the Agency's need for special government employees' services outweighs the potential for a conflict of interest created by the financial interest involved or when the interest of a regular government employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Based on today's agenda and all financial interests reported by Committee members and consultants, there has been one conflict of interest waiver issued under 18 U.S. Code 208 in connection with this meeting. We have the following consultants serving as temporary voting members: Dr. Bruce Gellin, Dr. Randy Hawkins, Dr. James Hildreth, Dr. Jeannette Lee, Dr. Ofer Levy, Dr. Wayne Marasco, Dr. Cody Meissner, Dr. Michael Nelson, Dr. Stanley Perlman, Dr.

Art Reingold, Dr. Mark Sawyer, and Dr. Melinda Wharton.

Among these consultants, Dr. James Hildreth, a special government employee, has been issued a waiver for his participation in today's meeting. The waiver was posted on the FDA website for public disclosure. Dr. Greg Sylvester of Seqirus will serve as the alternate industry representative for today's meeting. Industry representatives are not appointed as a special government employee 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 their participation in the meeting. They're voting members of the Committee. We have a large number of federal and non-federal speakers, as well as some guest speakers, and a responder today making various presentation on timely and relevant topics.

The following speakers and guest speakers for

this meeting have been screened for their conflicts of interest and cleared to participate on speakers for today's meeting. Dr. Ruth Link-Gelles, program lead, COVID-19 Vaccine Effectiveness, Epidemiology Task Force, COVID-19 Emergency Response Team at the Center for Disease Control and Prevention, CDC, Atlanta Georgia; Dr. Heather Scobie, Deputy Team Lead, Surveillance and Analytics, Epidemiology Task Force, COVID-19 Emergency Response Team, also at CDC, Atlanta, Georgia; Dr. Matthew Biggerstaff, epidemiologist, Influenza Division, National Center for Immunization on Respiratory Diseases, CDC Atlanta, Georgia, responder; Dr. Justin Lessler, professor, department of epidemiology, University of North Carolina, Chapel Hill, North Carolina; Dr. Stephan Hoge, President Moderna TX, Cambridge, Massachusetts; Dr. Gregory Glen, president, Research and Development, Novavax, Inc., Gaithersburg, Maryland; Dr. Kena Swanson, Vice President, Viral Vaccine, Vaccine Research and Development, Pfizer, Incorporated, New York, New York.

Additionally, we also have the following international guest speakers, Dr. Kanta Subbarao,

director, WHO, Collaborating Center for Reference and Research on Influenza, Doherty Institute for Infection and Immunity in Melbourne, Australia. Disclosure of conflicts of interests for speakers, guest speakers, and responders follow the applicable federal laws, regulations, and FDA guidance. FDA encourages all meeting participants, including open public hearing speakers, to advise the Committee of any financial relationships that they may have with any affected firms, its product, and if known, its direct competitors.

We would like to remind standing and temporary members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to inform the DFO and exclude themselves from the discussion, and their exclusion will be noted for the record. This concludes my reading of the conflicts of interest statement for the public record. At this time, I would like to hand over the meeting to our chair, Dr. Monto. Thank you. Dr. Monto.

FDA INTRODUCTION: CONSIDERATIONS FOR WHETHER AND HOW THE COVID-19 VACCINE STRAIN COMPOSITION SHOULD BE MODIFIED

DR. ARNOLD MONTO: Thank you, Sussan. I'd like first to introduce the center director of CBER, Dr. Peter Marks, who will go over the agenda and tell us what we are to discuss and the procedures for voting, et cetera, for the meeting. Thank you, Dr. Marks, for leading us in this very important direction.

DR. PETER MARKS: Yes, thank you very much, Dr. Monto. First of all, I want to welcome everyone to this meeting, want to thank those who are joining us as Committee members, as invited speakers, open public hearing speakers, as well as those members of the public who are tuning in. Today we'll be talking about considerations for whether and how the COVID-19 strain composition should be modified. We will be starting the meeting following my introductory comments with presentations from the Centers for Disease Control and Prevention on an update on the current epidemiology of

the COVID-19 pandemic and an update on the effectiveness of the COVID-19 vaccines.

Those presentations will be followed by a presentation on a modeling of the future epidemiology of the COVID-19 pandemic. Following a short break, we'll then have three sponsor presentations on clinical data regarding variant vaccines, and after that, there will be a WHO presentation on considerations of vaccine strain composition from the WHO group that considered this matter. And then we'll close out this morning's presentations with an FDA presentation on the data available for modified COVID-19 vaccine candidates and various considerations.

After our lunch break, there will be an open public hearing, and that will be followed by the Committee discussion of some questions that I'll show you in a few minutes, as well as a vote. And what I'd now like to do is just try to introduce this topic a bit here. Over the past two years we've seen waves of COVID-19 hospitalizations. Those have been associated with an evolution in the virus, and the virus has rapidly evolved through several different variants that

we have seen come and go.

What you are looking at on this slide are the various hospitalizations -- the number of hospitalizations during the Alpha wave, Delta wave, and Omicron wave. We don't see here, because this is the United States, the Beta variant which was also present in other locations outside of the U.S. Now, we've been very lucky in that we have several vaccines available in the United States that have been able to help us provide protection against SARS Coronavirus-2, the virus that causes COVID-19. Those include the two vaccines that are now approved in adults and are under emergency use authorization for other populations, that of Pfizer-BioNTech and that from Moderna.

There is a non-replicating viral vector vaccine from Janssen that is an adenoviral vector vaccine that is under availability for adults by emergency use authorization. And as people may be aware, on June 7th, we had a VRBPAC meeting during which we considered the Novavax vaccine -- a protein based -- a protein subunit-based vaccine for emergency use authorization.

These vaccines have undoubtedly saved many lives, and if you look globally at all of the COVID-19 vaccines, not just these, but the others that are available, this paper from *Lancet Infectious Diseases* is one of a number of different modeling papers that tries to estimate the number of lives saved, and it shows that it's likely that millions of lives have been saved globally by these vaccines. And in the United States it's clear that hundreds of thousands of lives have been saved by vaccinations.

Nonetheless, despite these vaccines helping us tremendously in reducing death and hospitalization, their effectiveness does appear to wane over time. That became clear about a year ago as effectiveness seemed to wane first in the oldest population and then also became clear that in the setting of new variants of COVID-19 that might emerge, the effectiveness might not hold up quite as well. And so, we had the initiation of booster campaigns with the idea that these booster vaccines could provide more durable immunity, particularly for certain populations such as older individuals and help prevent hospitalization,

death, and serious complications of COVID-19.

Even before we had the deployment of boosters, we anticipated that we might see an evolution in COVID-19, that would be the SARS Coronavirus would evolve to have new variants, and because of that we, in our guidance, put forth how to help develop vaccines that address new variants through immunobridging, that is looking at the immune response that occurred to these vaccines in clinical studies. We also noted that as we made, or if we made any switch of the vaccine composition, we'd have to think carefully about the potential implications of that switch for other variants that might need to be covered.

Most recently we've seen a relatively troubling rapid evolution of SARS Coronavirus-2. And the graphic you're looking at here will likely be updated by the Centers for Disease Control and Prevention as they show their presentation later on. But this is just to show you that since Omicron came on the scene at the beginning of this year, or a little before, we have seen the BA.1 variant, which was initially what Omicron was circulating as. It is now

no longer circulating; it has been eclipsed by other Omicron variants, and now what we're seeing is BA.2.12.1 as the primary variant, at least most recently.

But as you see at the lower right-hand corner, the green color is BA.4 and BA.5, the two newest variants to come up in large number, and they are increasingly taking over the share of COVID-19 disease that's been identified and the SARS Coronavirus cases that are being diagnosed. So, the concern here is that BA.4 and BA.5 will soon become the dominant variants present in the United States.

Our goal today is to try to address a situation that we are concerned about in the fall. We have a situation where roughly half of Americans have only received two vaccines to protect them against COVID-19. Other way put, half of Americans have not received a third dose, or a booster, and for those -- the other half that have there will also -- all of those individuals will have waning immunity as we move into the fall months of this year.

At that same time, we've seen this rapid

evolution of COVID-19 variants, and that will undoubtedly continue. And that combination of waning immunity, combined with the potential emergence of novel variants, during a time this winter where we will move inside as a population, increases our risk of a major COVID-19 outbreak.

And for that reason, we have to give serious consideration to a booster campaign this fall to help protect us during this period from another COVID-19 surge. I should say that right now we are in a bit of a plateau to slight increase for COVID-19 cases, most recently over the past few weeks averaging somewhere around 100,000 new cases reported per day with around 300 deaths and more recently having about 30,000 hospitalizations per day with a slight up creep in that number.

Now, our goal for trying to have the best possible match of the vaccine composition with what is circulating is to have the most effective vaccine. The better the match of the vaccines of the circulating strain we believe may correspond to improved vaccine effectiveness and potentially to a better durability of

protection.

And we are very much hoping that we would like to prevent death and hospitalization by the best choice that we make. But we also know that the better the match we have, we may go further down the list on the right here of this slide and not just prevent death and hospitalization but also potentially help reduce the amount of outpatient emergency care necessary and possibly reduce symptomatic infection.

Again, the most important things here, obviously, are preventing death and hospitalization, but to the extent that the match is best, we may go further down that list on the right. That's not anything special or specific to coronavirus vaccines. That's how most vaccines work in terms of the depth of protection.

So, what's our timeline for this? We had a VRBPAC meeting in early April -- on April 6th -- to discuss the general principles of booster vaccines, and that was very helpful in setting up some general principles that we might work through. And today we are having this meeting to help select a recommendation

for booster composition.

We will need to very rapidly move towards letting the companies know what that selection is because it takes several months to make these vaccines and then distribute them, and if we want these to be available by early fall, that will have to happen very soon. Over the summer we would anticipate the manufacturing of these vaccines, and hopefully by early October we would have the administration of booster vaccines.

Just to summarize, new variants of SARS Coronavirus-2 continue to emerge relatively rapidly. The protection against the existing variants from the prototype vaccines is less robust and wanes over time. We have had good protection against hospitalization and death in general, but it has waned over time, particularly in older individuals. Omicron is the latest and most transmissible variant to date, and BA.1 is no longer circulating in the United States. And BA.4/5 is poised to become the dominant variant.

We will hear today that vaccines against BA.4/5 are likely to cover BA.1. Small trials have

shown that vaccines to Beta, Delta, and Omicron BA.1 are mutagenic with no new safety concerns identified, and that may be relevant as we consider whether or not clinical data are necessary for moving to a new vaccine composition. And obviously, as I just noted, a decision is now needed on the variants to include for fall 2022. So, in terms of our discussion questions today, we'll have several discussion questions followed by a voting question.

So, we'll ask the Committee to provide input on the following questions. "Is a change to the current COVID-19 vaccine strain composition necessary at this time?" And we'll ask the Committee to "Please discuss the evidence supporting the selection of a specific Omicron sub-lineages such as BA.1 or BA.4, BA.5." We'll ask for discussion of whether a monovalent or bivalent vaccine is appropriate and ask the Committee to discuss the considerations for extrapolating the available clinical data for modified vaccines to different age groups, such as pediatrics.

And then there will be an additional discussion question on what additional data, if any,

would be needed to recommend an updated composition of the primary series vaccine, and if the booster vaccine composition changes, would continuing use of the prototype primary series vaccine this fall still be acceptable? And then we'll next have our voting question which is, "Does the Committee recommend inclusion of a SARS Coronavirus-2 Omicron component for COVID-19 booster vaccines in the United States." So, we'll look forward to this discussion today, and I will be able to take I think some questions for a few minutes.

DR. ARNOLD MONTO: Thank you, Dr. Marks. We have a few minutes now for questions about what we are to discuss and vote on this afternoon. We're going to try to keep totally to schedule because we need enough time to really have the robust discussion this afternoon. And I should make a comment that we're not coming up with a program this afternoon. We're not trying to be totally specific. We have certain discussion topics and a voting topic to decide on. So, questions for Dr. Marks, please.

I'm not seeing any hands raised. Are we

(inaudible).

MR. MICHAEL KAWCZYNSKI: They are, Arnold. Here, we've got the first one. Nope, we are.

DR. ARNOLD MONTO: Okay.

MR. MICHAEL KAWCZYNSKI: We have a couple up there. Here's the first one.

DR. ARNOLD MONTO: All right. I don't see any. Nothing's showing up on my screen. Dr. Gellin, I see you.

DR. BRUCE GELLIN: Okay. Thank you. Peter, thanks for the introduction. I wanted to focus on your timeline slide, which is probably the most important of all those, with plans for a booster campaign beginning in October. You mentioned about the time it takes to manufacture. We also know from -- when we were in these same committees for flu, we often hear about manufacturing timelines, and part of the advantage of particularly the mRNA vaccines are their nimbleness. Are we going to hear something about the manufacturing timelines, how long it takes to create a candidate virus, and in full scale manufacturing?

And then, also, on that timeline, it implies

that manufacturing doesn't start until we tell manufacturers what to do. And we know that manufacturers often manufacture at risk, and I hope that we can hear from the sponsors actually what they've already made that might be ready to go as soon as possible. Thank you.

DR. PETER MARKS: Thanks, Dr. Gellin. I believe we will hear from the sponsors what they may have made in their timeline. But just to give you a ballpark from speaking to multiple sponsors over time for the mRNA vaccines, it's probably about a three-month window from when they have some idea of what they're going to manufacture to when they can start to have product. That may not be that they will have the full amount of product for the booster campaign, but they will start to have that product.

And it is true that it's possible that much like for influenza, where manufacturers start to manufacture things at risk, that product has been manufactured at risk at this time, and I'd encourage us to -- for what we don't hear from the sponsors you can feel free to ask them as they are presenting.

DR. ARNOLD MONTO: Thank you. And I am now seeing hands. Dr. Marasco.

DR. WAYNE MARASCO: Hi, Peter. Thank you for taking questions. So, there's a lot of background papers that have come out in the last few weeks/months on immune imprinting and the effect of prior immunization or response to new antibodies to Omicron that develop. Are we going to hear data today to address that because it is the main concern here that we dampen the immune response when we're trying to improve it?

DR. PETER MARKS: I'm not sure about how much data we will hear. Perhaps after the presentations we can -- if we have a gap in knowledge here, we can see what we can do to help fill it with our folks, and if not, we can put that down as something we'll need to -- as a gap to fill. But I think there will be some discussion of this.

DR. WAYNE MARASCO: All right. Thank you.

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

DR. CODY MEISSNER: Thank you, Dr. Marks, for great summary. The question I have for you if it's

decided today that it would be helpful to change the composition of the vaccine but it's not clear if we need it right now, would one option be to store the vaccine in the strategic national stockpile similar to the way we do with (inaudible) ACAM2000? Is that an option?

DR. PETER MARKS: Dr. Meissner, I think it's a good question. I'm not sure how long we would actually have to store it. It may be that the manufacturers would be able to store it in their facilities just because I'm not sure that we would be storing it. I think you raised an excellent point. When would we need to deploy this? Would it be October/November? Could it be a little bit later?

I suspect that the manufacturers would store it for a time if it would -- and we'd have to ask them -- but my guess is if it was a matter of a few months, it would probably stay with the manufacturers. If it was a matter of long-term storage, I suspect you're right, the United States if it purchased this might take it into the strategic national stockpile.

But obviously that would be a discussion to be

had with an agency other than FDA, and so I can't promise that.

DR. CODY MEISSNER: Thank you.

DR. ARNOLD MONTO: Thank you. One last question from Dr. Lee.

DR. JEANNETTE LEE: Yes, so the discussion point I think has to do with boosters. Are we considering that as a recommendation also as initial vaccination? As you know there's a sizable proportion of the population that has not gotten vaccinated, not only in adults, but also children as well.

DR. PETER MARKS: Yep. Thank you, Dr. Lee. Absolutely, and I probably should've said it and emphasized it a little bit more. The second discussion question on that second slide really is going to focus on that so we'd like to discuss that. After initially discussing the booster question, we'd like you to go on to discuss about using a changed, or whether or not changed composition should be used for the initial vaccination. Thank you.

DR. JEANNETTE LEE: Thank you.

DR. ARNOLD MONTO: Thank you. But, Dr. Marks,

we are not going to be asking to vote on that issue. Is that correct?

DR. PETER MARKS: That's correct.

DR. ARNOLD MONTO: We are voting only on the issue of the booster.

DR. PETER MARKS: Correct. We will take back your recommendations and work through them on the initial vaccine.

CDC PRESENTATIONS: UPDATE ON CURRENT EPIDEMIOLOGY OF THE COVID-19 PANDEMIC AND SARS-COV-2 VARIANTS

DR. ARNOLD MONTO: Thank you, Dr. Marks. We now go to the CDC presentations. First, we will hear from Dr. Scobie, who will update us on the current epidemiology of the COVID-19 pandemics and the variants. Thank you. We're looking forward to hearing from you, Dr. Scobie, please.

DR. HEATHER SCOBIE: Thank you, Dr. Monto. Good morning. This graph shows the changing landscape of circulating variants by two-week period during January 2021 to January 2022. Prior to July 2021, many

variants had been circulating simultaneously, but this changed with the rise and displacement of previous variants by the Delta variant in orange, followed by the rise of the Omicron variant in purple in December of 2021.

The Omicron variant has six sub-lineages numbered BA.1, BA.1.1 and BA.2 through BA.5. Omicron has been shown to have increased transmissibility but decreased severity relative to previous variants, and Omicron has many mutations in the spike gene, as shown in the picture on the right, that are associated with lower vaccine effectiveness, a reduction in neutralization by sera from vaccinated or convalescent individuals, and a reduction in the efficacy of some monoclonal antibody treatments.

These are CDC data on the neutralizing activity of sera taken from people two to six weeks after completing an mRNA vaccine series against ancestral strains, pictured on the left in blue, and SARS-CoV-2 variants from Alpha to Omicron, pictured in the different colors on the right. Prior to the Omicron variants, the Beta variant shown in gold had

the largest full decrease of neutralization. Omicron, shown in teal on the right, had substantial reductions observed for the primary mRNA series against both BA.1 and BA.2.

Other recent publications have shown further reductions in neutralization related BA.2.12.1 and BA.4 and BA.5. This slide shows neutralization data at six to seven months after completing the second mRNA dose but before a booster dose on the left, and then two to six weeks after receiving a third mRNA dose on the right. After booster vaccination an enhancement in neutralizing antibodies was observed against SARS-CoV-2 viruses including Beta and Omicron variants. I note that the graph on the right has a broader Y axis than the graph on the left, making the improvement in titers from boosters even more pronounced than they appear.

Since Omicron became predominant, several monoclonal antibody treatments are no longer recommended as COVID-19 treatments due to reduced efficacy, including sotrovimab which was effective against BA.1 and BA.1.1, but substantially decreased against BA.2. Bebtelovimab can still be used for non-

hospitalized patients, and EVUSHELD is still recommended for pre-exposure prophylaxis in certain populations. But it must be given at a higher dosage. Oral antiviral therapeutics or small molecule inhibitors still retain an efficacy against the Omicron variant.

This is a graph of the number of SARS-CoV-2 sequences submitted globally to the GISAID public data repository since Omicron was first detected at the end of November 2021. Overall, the total number of submitted sequences globally has shown a declining trend since January 2022. The blue color shows the delta variant was displaced by the BA.1 -- the Omicron BA.1 sub-lineages -- shown in red, salmon, and pink colors -- followed by the rise of the Omicron BA.2 sub-lineages in orange, brown and peach. And BA.4 and 5 sub-lineages are shown in yellow.

This is a graph of the same data but now with the variant sub-lineages expressed as the proportion of the overall total of submitted sequences over time. Most notably, you can see on the right side of the graph that BA.4 and BA.5 sub-lineages in the yellow

colors represent an increasing proportion of submitted sequences while the proportions of BA.2 sub-lineages have been declining.

This stacked bar graph shows recent U.S. trends in the national weighted estimates of variant proportions and now cast projections of circulating SARS-CoV-2 lineages by week of specimen collection from CDC's COVID Data Tracker. Omicron sub-lineages depicted in different purple, pink, and teal shades have been over 99 percent predominant for many months now.

The BA.1.1 sub-lineage in dark purple was gradually displaced by the BA.2 sub-lineage shown in lavender and more recently the BA.2.12.1 sub-lineage in salmon which were 9 and 56 percent of circulating lineages respectively as of the week ending June 18th. The BA.4 and BA.5 sub-lineages in the teal colors comprised 11 and 24 percent for the same time period.

This map shows the relative proportions of the Omicron sub-lineages, BA.2.12.1 in salmon, BA.2 in lavender, BA.5 in dark teal, and BA.4 in light teal across the ten health and human services regions.

BA.2.12.1 represented at least 49 percent of circulating lineages in all regions during this time period.

This is a graph of COVID-19 cases reported globally by World Health Organization regions in the different colored stacked bars and globally reported deaths represented by the solid navy line. There were over 536 million confirmed cases and over 6.3 million deaths as of June 19th, 2022.

This graph shows the trend in the daily numbers of COVID-19 cases reported in the United States since the beginning of the pandemic. The number of cases associated with the Alpha variant were relatively small compared with the Delta and Omicron variants. Nationally reported cases showed increasing trends in April and May and then have leveled off in June. I note that the actual number of cases is underestimated due to the increased use of at home tests which are largely unreported to public health departments. As of June 23rd, there've been over 86 million COVID-19 cases reported in the U.S.

This is a graph of trends of infection induced

SARS-CoV-2 antibodies by age group from CDC's national commercial laboratory seroprevalence study. The percentages of the people with previous infection noticeably increased following the rise of the Omicron variant in late December. Compared with older age groups, greater seroprevalence was noted in younger age groups which is likely related to these younger groups having later eligibility for vaccination and different exposure risks. Nationally estimated seroprevalence during February 2022 was 58 percent.

These are the weekly trends in the rates of new COVID-19 in-patient admissions by age group. Higher hospitalization rates occurred in the older age groups, with patients aged 70 plus years in the solid purple line, and 65 to 74 and 50 to 64 years in the dashed pink lines, having the highest admission rate, followed by other adult age groups in shades of blue. On the right you can see that recent increases in hospitalization rates have been driven by older age groups, especially patients aged 70 plus years.

This graph shows the trends in the daily number of COVID-19 deaths reported in the United States

since the beginning of the pandemic, including during the waves associated with the Alpha, Delta, and Omicron variants. Even though Omicron infections are generally less severe overall relative to Delta, the number of deaths related to Omicron was relatively high because Omicron case numbers were very high. As of June 23rd, there have been over 1,010,000 deaths due to COVID-19 reported cumulatively in the U.S.

These are the weekly trends in COVID-19 associated mortality rates by age group. The data show that higher mortality rates are also consistently observed in older age groups, most notably on this graph those age 75 plus, 65 to 74, and 50 to 64 years as shown in the purple and pink colors. When you zoom in on the right side of the graph, you can see a recent increase in death rates for older ages similar to hospitalization trends by age, especially for ages 75 plus years.

A preprint analysis estimated that for the one million COVID-19 deaths reported in the United States as of May 12th, 2022, about 46 percent of deaths were attributed to SARS-CoV-2 variants versus the ancestral

strain. And about 27 percent of total deaths were attributed to Delta and 12 percent to Omicron. Since May 2020, 8,525 cases of multisystem inflammatory syndrome in children and 69 deaths have been reported in children related to this condition after COVID-19.

According to a recent MNW article published by CDC, one in five COVID-19 survivors aged 18 to 64 years and one in four survivors over 65 years experienced at least one new chronic condition that might be attributable to previous COVID-19 infection. Adult COVID-19 survivors also had twice the risk for developing pulmonary embolism or respiratory conditions. This study used electronic health records to study a population who received medical care for COVID-19 illness, possibly indicating that they had more severe symptoms, which could theoretically result in higher rates of post COVID-19 conditions.

As of June 23rd, more than 222 million people in the U.S. have been vaccinated with a primary vaccine series, which is 71 percent of the eligible population aged five years or older. There are over 105 million people, or 49 percent of the population, aged 12 years

or older who have received a first booster dose and about 17.4 million people, or 26 percent of the population aged 50 years or older, who have received a second booster dose.

These figures show trends over time and by age group and the percentage of people who have received at least a primary series on the left and a booster dose on the right. In both figures vaccination coverage is higher in older age groups indicated in the purple and pink colors. We can also see that coverage with the primary series for ages 5 to 11, as shown on the right with a yellow dotted line, is still relatively low at 30 percent. Booster coverage on the right remains under 50 percent for age groups less than 50 years shown in blue and yellow colors.

Next, we're going to shift to consider surveillance monitoring of vaccine breakthrough. To monitor rates of COVID-19 cases and deaths by vaccination status, CDC collaborates with 31 public health jurisdictions representing 70 percent of the U.S. population that actively link case surveillance, immunization registry, and vital registration data.

CDC tracks rates of COVID-19 hospitalization by vaccination status using COVID-NET, a population-based sentinel surveillance system in 99 counties and 14 states, representing 10 percent of the U.S. population.

We also have detailed data on serious illness in vaccinated persons through COVID-NET, as well as electronic health record and vaccine effectiveness platforms. CDC's vaccine effectiveness studies allow for more robust analyses as compared with surveillance and a better understanding of how well vaccines are working.

This slide shows the age adjusted rates of COVID-19 cases by vaccination status. In May, unvaccinated people ages five years and older had two times higher risk of testing positive for COVID-19 compared to people vaccinated with at least a primary series. This graph shows the age adjusted rates of COVID-19 associated hospitalizations by vaccination status and receipt of a booster dose. Hospitalizations for COVID-19 were higher among unvaccinated than vaccinated people over time, including after Omicron became the predominant variant. In May, unvaccinated

adults ages 18 years or older had 3.5 times higher risk of COVID-19 associated hospitalization compared to those vaccinated with a primary series and booster dose.

This slide shows age adjusted rates of COVID-19 associated deaths by vaccination status and receipt of booster doses. Unvaccinated people in all age groups had higher mortality rates than people who received a primary series alone or people who received a booster dose, including after Omicron became predominant.

Unvaccinated people, ages 12 years and older that were diagnosed in April, had eight times the risk of dying from COVID-19 compared to people vaccinated with a primary series and booster dose. This represented a decrease in the rate ratio from March, which was 17 times greater in unvaccinated people versus those with a booster dose. This is possibly related to waning immunity in older age groups and increased community transmission of the Omicron BA.2 sub-lineage as well as other factors.

In an early analysis of data on second

boosters among people ages 50 years and older diagnosed with COVID-19 in April 2022, unvaccinated people had 42 times the risk of dying from COVID-19 compared to those who received two booster doses. Further, people vaccinated with one booster dose had four times the risk of dying from COVID-19 compared to those having two booster doses.

These data suggest that getting a second COVID-19 vaccine booster can further enhance or restore protection that might've decreased over time after receiving the last vaccine dose. Various studies have shown that severe COVID-19 illness is relatively rare among vaccinated people compared with unvaccinated people. Most vaccinated people who get severe COVID-19 illness have multiple risk factors, including older age and underlying medical conditions, including immunosuppression, diabetes, and chronic kidney, lung, cardiovascular, or neurologic diseases.

To help mitigate illness, uptake of COVID-19 antiviral treatments is important. Among adults ages 18 years and older surveyed with recent SARS-CoV-2 infection in New York City during BA.2 and BA.2.12.1

surge at the end of April and May, 29 percent of people infected had risk factors making them eligible to receive the antiviral paxlovid. Among those diagnosed with COVID-19 by a healthcare provider, 55 percent were not aware of the drug, and only 15 percent reported receiving it, whilst 3 percent had reported being unable to access it. Reported receipt was lower among people who were ages 65 years and older, non-college graduates, and unemployed.

In summary, CDC continues to monitor emerging variants like the sub-lineages of Omicron including their prevalence and impact on disease incidence and severity over time. Monitoring rates of cases, hospitalizations, and deaths by vaccination status has been helpful for monitoring the impact of different variants. Currently authorized vaccines offer protection against infections, severe illness, and death, so it's important to stay up to date with vaccination including receipt of first and second booster doses in the eligible populations.

Finally, there's a need to educate prescribing clinicians as well as to promote awareness and uptake

of antiviral drugs among individuals at risk of severe COVID-19 illness.

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

DR. ARNOLD MONTO: Thank you very much for your clear presentation and challenging our ability to recognize different shades and colors. Questions please. We have a few minutes to clarify some of the critical points that have been made. Dr. Meissner.

DR. CODY MEISSNER: Thank you again for another very clear and helpful presentation. I'd like to go back to your -- and ask a question about your slide regarding MIS-C, and there was a recent report from Denmark noting that the rates of MIS-C following Omicron are much lower than the rates following Delta, for example. And looking at the data from CDC on data tracker it seems as though that's also the case here in the United States. Do you think that's an accurate statement?

DR. HEATHER SCOBIE: So, I don't have, unfortunately, that broken out by different wave of variants, so I don't think I can answer your question

well enough. But I can maybe get back to you with that by the end of the day?

DR. CODY MEISSNER: Thank you.

DR. ARNOLD MONTO: Thanks. Dr. Reingold, followed by Dr. Hawkins.

DR. ARTHUR REINGOLD: Yeah, hi. Just a quick question. Your summary slide, I believe you said that the vaccines continue to protect against infection, and I don't recall you showing data about the reduced infection. And I'm wondering if that's what data we have on the effect of vaccination on infection rather than severe illness and (audio skip). Thanks.

DR. HEATHER SCOBIE: So, I showed this one slide, and this is looking at COVID-19 cases which are basically people who test positive for COVID-19, either using a PCR test or a rapid antigen test. And it does show that people who are vaccinated have two-fold lower chance of testing positive for COVID-19 in these kind of crude surveillance data. And Dr. Link-Gelles is going to also show data from vaccine effectiveness studies which are, of course, more robust analyses where you can control for different factors, and she'll

also be able to speak to the VE against infection and symptomatic illness.

DR. ARTHUR REINGOLD: Thanks.

DR. ARNOLD MONTO: Thanks. Dr. Hawkins.

DR. RANDY HAWKINS: Yes, this observation we see epidemiological information. So, I'm as a primary care physician private practicing inner city, really in the last month have seen significant increases in symptomatic COVID infections in folks who qualified for antivirals but not sick enough to be hospitalized, and majority of those have had at least one booster and this in the primary series. So, we're spiking in inner city.

Unfortunately, also, I'm having a pessimistic acceptance of the vaccines in people who have never had a primary series, despite close relationship. They still come to see me. Those who have not accepted the vaccine ever are not influenced and accepting the vaccine now, some which have had infection, and, of course, they survived because they're still coming into the office. Any comments or observations about that? And also, we haven't been able to get 100 percent of

antivirals in our community in Los Angeles County. It was lesser statistic in May. Thank you.

DR. ARNOLD MONTO: Thank you.

DR. HEATHER SCOBIE: Yeah, so I'm not sure -- sorry. I'm not sure what age group you're talking about, but we do have the observation that you can see it in the surveillance data that isn't by vaccination status, that we have increases in both hospitalization rates in older ages and then deaths in older ages during the most recent BA.2 wave. And we're also seeing in the surveillance data both the hospitalizations by vaccination status, which the rate ratio has gone down in recent months. So unvaccinated people have 3.5 higher risk of hospitalization compared to those with one booster dose, but this rate used to be higher. And it's also true for deaths as well.

So, there's been a big dip in the rate ratio. And the best sense that we can make of that is older people are largely the people that are hospitalized, and unfortunately, they make up the majority of people who pass away from COVID as well. And the majority of these folks received their boosters in September and

October, so it's really already been six to seven months since a lot of them received that booster dose.

And as you know, as I also showed, we've had rather poor uptake of second boosters, and that's kind of the bright story of what I presented is just that the second booster doses, from what we see so far in this early analysis, they're protecting very well. So, they're taking down that risk again -- the risk of death. So, we need to really, I think, in the meantime be pushing the second boosters in older ages to protect against serious illness.

I'm not sure if that addresses your question or not.

DR. RANDY HAWKINS: More than anything wanted to highlight the conditions and problems that still exist that brings us here and just my concern about the fact that still haven't been able to get -- many people in the practice who have not received their primary series still won't do it even though they're seeing the spike and have all kinds of excuses for that. Thank you.

DR. HEATHER SCOBIE: Mm-hmm. Yeah.

DR. ARNOLD MONTO: Thank you, Dr. Kim, followed by Dr. Gellin, and then we will switch over.

CAPT. DAVID KIM: Thanks for that terrific discussion. You've showed a lot of information on the burden of COVID based on age. Do you have similar breakdown of data on race and ethnicity, particularly for the older population?

DR. HEATHER SCOBIE: So, I didn't show that in the slides, and I don't have that prepared for you. But it does exist on the COVID-19 data tracker. If that's something that's desired by the Committee, I can also get you a slide with that by the end of the day.

DR. ARNOLD MONTO: Can you summarize without showing data about what the relative proportions are?

DR. HEATHER SCOBIE: I can't summarize off the top of my head. I know that there have been some changes that have occurred over time with -- basically like with vaccination trends have also occurred over, time and I presented some of that last time. So, we have no longer appearing in terms of people are getting vaccinated to be an access issue but a personal preference issue. So, there have been changes both in

the vaccination rates by race and ethnicity and also who is having serious illness.

DR. ARNOLD MONTO: Thank you. Let's go on finally to Dr. Gellin.

DR. BRUCE GELLIN: Yeah. Thanks for that. I've been squinting on the right-hand side at your many curves. Most of them go through April, maybe one through May. I'm interested if we have any information about the impact of BA.4 and 5 on these same things, severe hospitalization -- severe disease, hospitalization, and death.

DR. HEATHER SCOBIE: So, the surveillance data not by vaccination status goes through the most recent date, so it would -- I guess I see why you're confused because it's a labeling issue. But these data do go through almost the current date. Like this graph goes through June 25th, and the shaded portion of the graph would, of course, be where there's a reporting lag so that's less reliable information.

So, there is maybe an issue with labeling of the axis, and then the data on cases, hospitalizations and deaths by vaccination status, there is a larger lag

associated with those data because they have to be linked back to immunization registry data, vital registration data. So, we do give health departments time to perform that linkage and for the more serious outcomes, like hospitalization and death to occur as part of the natural disease progression. I don't know if that helps.

DR. BRUCE GELLIN: Actually, I was interested in the sub-lineage piece of it, how much of that may be related to 4 and 5.

DR. HEATHER SCOBIE: Oh, BA.4 and Ba.5. Okay. So I think CDC is still -- we're still at 35 percent combined for BA.4 and BA.5, so we wouldn't consider those to be predominant yet. But we will be watching this closely as these lineages gain hold, and we are projecting that they will continue to increase. And we're not projecting or predicting that this will be a major shift in the pandemic, but we are characterizing those strains and watching closely to see what happens.

DR. ARNOLD MONTO: Thank you. And, yeah, I know you're watching what's going in in the rest of the world as well.

UPDATE ON THE EFFECTIVENESS OF COVID-19 VACCINES

DR. ARNOLD MONTO: Next, we switch to Dr. Link-Gelles who will give us the critical update on the effectiveness of the COVID-19 vaccines. Dr. Link-Gelles.

DR. RUTH LINK-GELLES: Good morning. Today I'll be sharing updates on COVID-19 vaccine effectiveness during Omicron. Updates on VE in children and adolescents were shared recently with VRBPAC, so today I'll be primarily focusing on VE in adults. Although, I do include a couple of slides on children and adolescents just for completeness. As with previous presentations, I've organized this presentation by increasing severity of outcome, starting with infection, then emergency department and urgent care visits, and then hospitalizations.

Starting with infection, I'll start with CDC's HEROES-RECOVER platform. This is a prospective cohort study in frontline and other essential workers that includes weekly swabbing regardless of symptom status

and so should not be impacted by changes in testing practices due to the availability of home tests. This study of the Cox proportional hazards model with adjustment for propensity to be vaccinated, site, SARS-CoV-2 circulation in community mask use. Individuals with prior infection were excluded from the analysis presented.

Here we have VE against infection separated by time since last dose. Note that most vaccinated participants in this cohort were fully vaccinated by early to mid-2021 and therefore did not contribute to Omicron VE estimates less than 150 days from the second dose. And so, we've admitted that estimate as confidence intervals were too wide to interpret.

We can see an increase in VE in the early post-third dose period with lower VE and a wide confidence interval at greater than 150 days since the third dose. Based on the timing and receipt of the third dose in this cohort, three dose estimates include predominantly BA.2 and BA.2.12.1 cases which likely explains the lower VE in the greater than 150 days after a third dose, compared to the same time frame

after the second dose which was predominantly BA.1.

Moving on now to the Increase in Community Access to Testing, or ICATT platform, which is national community-based drive through testing data from pharmacies. This platform relies on self-reported vaccine history and uses a test negative design where cases or persons with at least one COVID-like symptom and a positive NAAD test in controls are symptomatic with a negative NAAD test. Models are adjusted for variables shown here.

Adolescents were tested December to May with a mix of BA.1, BA.2, and BA.2.12.1 circulation. Adults were tested in April and May, which was a mix of BA.2 and 2.11.1. This is VE among adolescents 12 -- sorry, this is VE among adolescents 12 to 15 years of age. In the black, we show two versus zero doses, which wanes to zero VE against infection by three months after the second dose. In blue, we have the relative VE of three doses compared to two doses which starts a bit higher than the two versus zero VE and does not go quite as low.

Now moving onto adults, this slide shows only

relative VE for three versus two doses among adults 18 to 49 years in black and 50 to 64 years in blue. As with adolescents, we see waning against infection after the third dose with VE appearing to plateau around 10 to 20 percent.

In summary, for infection we see that a third dose provides additional protection over two doses, although waning is evident during Omicron even with a third dose, which may be partly attributable to prior infection as well as the presence of BA.2 and 2.12.1 during the third dose follow up. Patterns of mRNA VE wax and waning by time since last dose looks similar across age groups.

Now, moving on to emergency department and urgent care visits. The VISION Network is a multi-state network based on electronic healthcare records. Like ICATT, it uses a test negative design with cases having CLI and a positive PCR and controls having CLI with a negative PCR. VE is adjusted for propensity to be vaccinated, weight, calendar time, region, local virus circulation, and age in vaccination is determined via healthcare records and state and city vaccine

registries.

This is an update to data included in the Cline et all MWR in March showing VE against emergency department urgent care for 5 to 11 on the top and adolescents 12 to 15 on the bottom. So, the 14 to 59 days after the second dose, we see almost identical VE point estimates in the two groups, 50 to 56 percent with wider confidence intervals for the adolescents since it's been much longer since they were recommended to be vaccinated. The adjusted VE drops substantially for adolescents 60 days after vaccination.

On the bottom of the slide, I've noted the case definition for an ED/UC visit, which highlights here the potential for inclusion of children visiting urgent care and EDs with COVID instead of for COVID. Like we have bigger concerns for kids than adults as the case definition includes GI symptoms, which may have many frequent non-COVID causes in kids and could potentially drive the VE estimates for ED and UC visits closer to those for infection in kids.

As with infection, a booster dose provided significant increase in VE among 12- to 15-year-olds,

73 percent, up to a median of 58 days after the booster. Here we see VE divided by variant predominant periods in the VISION network among immunocompetent adults over 18 years with BA.1 on the top and BA.2 and 2.12.1 on the bottom. VE by time since the second dose is shown in green. VE by time since the third dose is shown in blue, and early post fourth dose VE estimate for adults over 50 years of age are shown in black for BA.2 only due to the timing of the recommendation for the additional booster dose. We see lower VE overall and more pronounced weaning during the BA.2 and 2.12.1 predominant period for the fourth dose among older adults restoring protection to what was seen after the third dose.

Moving on now to hospitalization. Here we again show VISION network data from immunocompetent adults 18 years of age and up, this time with VE against hospitalization. As in earlier variant periods, we see substantially higher VE against hospitalization than we did against ED/UC visits for infection. As with ED and UC visits, there seems to be an indication of slightly lower VE during the BA.2 and

2.12.1 predominant period with a fourth dose restoring protection to that shortly after the third dose.

Here we show all Omicron combined divided by age groups 18 to 49 years, 50 to 64 years, and 65 plus years for VE against infection. We can see high VE in the 7 to 59 and 60 to 119 days after the third dose with a drop in VE during the 120 to 179 days since the third dose, which likely includes more BA.2 and 2.12.1 cases than the earlier time periods.

Here we show the same data, this time for immunocompromised adults during Omicron. We see a similar pattern here with more waning during increased time since the third dose compared to immunocompetent, emphasizing the need for an additional primary series dose and additional booster dose in this population.

Finally, I'll share data from IVY platform from December 2021 through May 2022. Adults ages 18 and up from 21 medical centers in 18 states are enrolled. Cases have COVID like illness and a positive PCR antigen test and the controls have CLI and a negative PCR. Here we see VE by age group and number of doses received among immunocompetent adults with two

dose VE in green and three dose VE in blue. Patterns are similar across age groups with higher VE for three doses compared to two doses, although note the much shorter follow-up time after the third dose compared to the second dose.

This is, again, the same analysis but now among immunocompromised adult individuals with early fourth dose data shown in black for overall. Although follow-up time after the fourth dose is short and the CI was somewhat wide, it does appear to provide additional protection beyond the third dose. Due to small sample sizes in the older age groups, we are not able to split out fourth dose estimates by age.

In summary, VE was lower during Omicron compared to Delta, although the third dose provides more protection than the second dose for all outcomes. VE appears lower during BA.2 compared to BA.1, which may be attributable to differences in prior infection between the BA.1 and BA.2 time periods, as well as the potential for a decreased neutralization against BA.2.12.1. Patterns were similar across age groups, and while it's too early to draw conclusions about the

fourth dose in the overall population, it appears to provide substantial additional protection among immunocompromised individuals, emphasizing the need to stay up to date on all recommended booster doses.

I'd like to acknowledge the individuals shown on this slide, and I'm happy to take questions.

DR. ARNOLD MONTO: While we wait for questions can you tell us about other experiences in other parts of the world? I know that's -- you probably don't have PowerPoints prepared, but there's the .4 and .5 have been ahead of us in some parts of the world such as South Africa. What's your impression of the data they're seeing?

DR. RUTH LINK-GELLES: Sure. So, I think it's important to keep in mind that every country has had different patterns of waves. So, for example, the UK has seen similarities between their BA.1 and BA.2 vaccine effectiveness, whereas we're seeing some differences, and I think a lot of that is attributable to different timing of the waves. So, it's a bit hard to compare and extrapolate. For BA.4 and 5, I think there is data showing decreased neutralization

antibodies, and so it's likely that VE would be somewhat decreased compared to BA.1. But I think it will remain to be seen the impact in the U.S. of the large wave of BA.1 prior infection as well as the ongoing wave of BA.2 and the impact that'll have on vaccine effectiveness during BA.4 and 5 in the U.S.

DR. ARNOLD MONTO: So, if I could summarize what the situation right now is that most of our data about .4 and .5 is based on immunology. Looking at neutralizing antibodies and trying to predict from those what we are going to see when we have sufficient numbers.

DR. RUTH LINK-GELLES: Yes, that's correct.

DR. ARNOLD MONTO: Okay. Dr. Perlman.

DR. STANLEY PERLMAN: Yeah, I actually had a follow-up question on Dr. Monto's question. So, can you take all these data, and which mostly right now are observational -- they show we get vaccination and then there's waning immunity and waning efficacy. Is it possible to assume a given desirable level of vaccine efficacy and then do modeling to try to answer the question when boosting should be done? It may be very

complicated, but I assume there are ways to do that using modeling procedures that are here now and quit making various assumptions.

DR. RUTH LINK-GELLES: Yes, and I believe, actually, that the next presentation or presentation later today will cover some modeling scenarios for the fall, incorporating both different levels of vaccine effectiveness, prior infection, masking, other scenarios like that.

DR. STANLEY PERLMAN: Thank you.

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

DR. HAYLEY ALTMAN-GANS: Hey, thank you so much. This may be a question more for Dr. Scobie, I don't know, but I'm wondering in the uptick of the hospitalizations -- and so could be breakthrough for you in terms of vaccine efficacy -- are we doing the strain specifics for those? I mean, hospitals should be looking at that, so are those pulling out the BA.4/5 as opposed to those who maybe are maintaining a little bit of protection for the main strains that are dominant right now?

DR. RUTH LINK-GELLES: You're talking about

specifically in the surveillance data that Dr. Scobie showed? I'm not sure --

DR. HAYLEY ALTMAN-GANS: Yeah. So, in terms of what that uptick is showing, have those been identified which variants they are?

DR. RUTH LINK-GELLES: I'm not sure if Dr. Scobie is on and can answer that, but generally the case surveillance data includes all data from the states that participate. And so it's not necessarily all sequenced. It looks like Scobie has stepped away. But so essentially some hospitals sequence, not all hospitals do, and so the overall case surveillance data includes all cases identified in that jurisdiction, not just those that are sequenced.

So it's a little bit hard to parse out specifically whether the uptick is BA.4 and 5 alone. I think based on the sequencing data that we have seen, and just the general trends that we've seen with BA.1 and BA.2 and the decreasing proportion of cases that are BA.2, it's likely that the current trends, the current uptick, would be due to BA.4 and 5 since those are the only sequences that are increasing in

proportion in the U.S. right now.

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

DR. ADAM BERGER: There we go. Okay. Thanks so much for the presentation. And what I'm wondering about, so all the data is shown off of the two-dose primary series. And I'm just wondering -- I know we're generally talking about Pfizer or Moderna when we're talking about this -- but I'm wondering about the J&J series for those that only took a single dose and then received boosters, if there's any data being collected for those that just received the single dose and whether there's any differences in the data that you're presenting here.

And I do recognize that we are talking about a much more limited set of total population that received the J&J dose as the primary.

DR. RUTH LINK-GELLES: Sure. I didn't include the J&J information here, but I presented it, I think, back in April to VRBPAC. And so there is some data that we published out there looking at J&J alone, two doses of J&J, one dose of J&J, and one dose of an mRNA versus a three-mRNA series. And generally, we see

lower VE across the board for series that include a J&J dose, with two doses of J&J being the lowest overall VE compared to a J&J and an mRNA or three mRNA doses.

DR. ADAM BERGER: Has that continued to be tracked during the same time period that you have here as well? Does that data still play out or is it decreasing at all over time?

DR. RUTH LINK-GELLIN: It does continue to be tracked. We haven't shown it because the confidence intervals are so wide that it's a bit hard to interpret, and that's just due to small numbers. The number of individuals that initially got a J&J and therefore would be eligible for one of the J&J containing series was small overall, and then as with the mRNA series we've seen drop-off with each additional booster. And so there're just not that many individuals out there that have gotten a J&J plus an mRNA and has continued to be eligible for additional booster doses.

DR. ADAM BERGER: Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Marasco, followed by Dr. Pergam.

DR. WAYNE MARASCO: Yes, Dr. Link-Gelles, thank you very much. You've shown a slide with vaccine effectiveness for ER visits for immunocompetent adults greater than 18, and in that you show differences in vaccine effectiveness during the BA.1 period versus the BA.2 period at intervals greater than 120 days and they're pretty significant differences between those groups. Can you comment on that, why you think that is the case?

So greater than 120 days, three doses of BA.1 versus three doses of BA.2. You're down to 25, 30 percent in one case and as high as sort of 80 percent in the other. Is that data -- and they're comparable number of people, so is that really because of the type of immune antibodies that were getting elicited or a change in the rate of decay of the protective antibodies?

DR. RUTH LINK-GELLES: I think there are likely a couple of things going on. I think that single biggest contributor is different patterns of prior infection. So just because of the timing of when BA.1 and BA.2 were seen, individuals had far more prior

infection during the BA.2 era than the BA.1 era, and we know that having a lot of prior infection in the unvaccinated population decreases VE because your unvaccinated population has some protection from prior infection. So it makes vaccine look less effective.

And so, we think that there is probably a lot more undocumented prior infection during the BA.2 period compared the BA.1 period, and so that's likely a big chunk of what we're picking up on here, that more unvaccinated people during the BA.2 period had a prior infection and therefore had some level of protection which dampens overall VE.

The other piece that I think may contribute but probably is a smaller bit is that for BA.2.12.1 in particular there is lower levels of neutralizing antibodies compared to BA.1 and 2, and so both BA.2 and 2.12.1 circulated at the same time in the U.S. And so we can't parse out VE for those sub-lineages separately, so we've had to combine them here. But I think the contribution there of 2.12.1 with lower neutralizing antibodies is likely contributing to this as well. But, again, I think the single biggest

contributor is probably different patterns of prior infection.

DR. WAYNE MARASCO: Thank you.

DR. ARNOLD MONTO: Dr. Pergam.

DR. STEVEN PERGAM: Thanks, Dr. Link-Gelles. I wanted you just to remind us about the current availability of sequencing in general because one of the challenges in one of the slides Dr. Scobie demonstrated was the decreasing number of cases being submitted to GISAID, and I think part of that is decreasing numbers overall. But is that also a reflection of, as many have mentioned, increased use of home tests and decreasing numbers of samples that are being sent in?

And you have a lot of sentinel sites and looking at this similar to the way we have with flu, but I'm curious what is the -- can you give us a little bit of data about the number of sequences you're getting, how often they're being looked at, because I think it'll be really important as we get into new waves how quickly that data's coming forward for us to be able to assess for these new vaccine strains.

DR. RUTH LINK-GELLES: Yeah, absolutely. So, I think Dr. Scobie can probably speak to the first part of your question around the number of sequences that we're getting in the Q&A this afternoon, but I will say home testing -- I think the effects of home testing on our surveillance and our vaccine effectiveness data are really quite extensive and have changed the patterns a lot over time. If we think back to December and January when it was very hard to get a home test, most people were still going to labs to get PCR tests, and so we were able to sequence more of that data.

As home tests have become more prevalent, both the sequencing has become more difficult as well as ascertainment of prior infection, which as I mentioned in the answer to the previous question can affect our estimates quite a bit. But I can ask Dr. Scobie to circle back during the Q&A this afternoon about sequencing.

DR. STEVEN PERGAM: Yeah, and then just a quick follow-up to that is is there any sense that the people that are getting PCR testing or potentially the more severe cases versus those who are getting home

tests or potentially those who are not as severe? Have you guys been looking at any of that in terms of the estimates for severity with these different strains?

DR. RUTH LINK-GELLES: Yeah, I think that that's likely the case. I mean, if you just think about the way hospitals test almost universally when they hospitalize an individual, and of course, bigger medical centers are more likely to have access to sequencing. I think there is likely a bit of a difference between people that are getting PCRs versus home tests.

DR. STEVEN PERGAM: Thank you.

DR. ARNOLD MONTO: But in terms of the networks you're reporting, these networks are sequencing, correct?

DR. RUTH LINK-GELLES: Not all networks. So, the HEROES RECOVER cohort study that I showed at the beginning, that one does do sequencing of all positive cases as long as their CT value allows it. The increase in community access to testing, the pharmacy testing data does not sequence the majority of their cases. VISION is an electronic health care record-

based system, so we don't generally have sequencing data. And we use time to determine the likely variant. IVY does do sequencing, so it really just depends on how the system is set up whether it's going to include sequencing data or not.

DR. ARNOLD MONTO: Because that is one of the few ways we can be sure that we're not -- that we don't have sampling bias in terms of those who get sequenced and those that don't in these networks, correct?

DR. RUTH LINK-GELLES: Sure, I guess (inaudible). For the VISION network, what we've done is said that in a single site when the majority of the sequences -- sorry, when more than 75 percent of the sequences are given variants, we call that the variant predominant period. So, when BA.1 was more than 75 percent we start counting those as BA.1 cases. When it drops below 75 percent, we start a washout period of a couple weeks, and then as BA.2 rose in predominance, when BA.2 was more than 75 percent of all sequenced cases in a site, we start counting as BA.2 cases.

MODELING FUTURE EPIDEMIOLOGY OF THE COVID-19 PANDEMIC

DR. ARNOLD MONTO: Thank you. We now go on to hearing about the modeling of future epidemiology of COVID-19 pandemic. Dr. Justin Lessler from the University of North Carolina. Dr. Lessler.

DR. JUSTIN LESSLER: Hi, yes. So, I am presenting on our round 13 projections -- scenario planning projection from the COVID-19 Scenario Modeling Hub, projecting burden between March 2022 and March 2023. These are projections that were made in mid-March and are under current vaccination policy, and I'm presenting on behalf of this COVID-19 Scenario Modeling Hub, which is the collaboration from many groups. And I'd particularly like to credit those groups that have presented a model.

To start with just a few disclaimers, this is independent work of the COVID-19 Scenario Modeling Hub and does not reflect the views or work of the CDC or any other institution. I'm funded under multiple CDC grants for epidemic modeling of emerging national and global infectious disease threats, including SARS-CoV-

2. If there are any questions regarding the CDC's views on this work, Dr. Matthew Biggerstaff is here to respond to this.

So, first what is the COVID-19 Scenario Modeling Hub? So, this is a multi-team effort aimed at creating and modeling planning scenarios of the mid to long term COVID-19 situation. We project cases, hospitalizations, and deaths, and I will be focusing primarily on hospitalizations throughout this presentation. The scenarios are developed in close collaboration with government agencies and other stakeholders. To date, we've done 13 rounds of projections, 11 of which are public. One was a practice round, and one was rendered invalid by the emergence of Omicron before we released it.

Six to ten teams submit models per round at the national level. We do have some more state models, and results are ensembled and summarized by the Hub. Here you can see a graph of our first -- that has our first 12 rounds of projections -- well, ten that were made public -- with the gray being the actual course of the pandemic in terms of hospitalizations and the

colors being projections from the (inaudible).

So, to get started, I want to clarify what a scenario is. You'll notice I'm not saying forecast. I'm saying scenario, and I think the reason we focus on scenarios is captured by this quote from Alessandro Vespigani that "Models are not oracles and models providing answers that are conditional uncertain assumptions."

So, when we try to project out for more than a few weeks, I think we can look out and do proper forecast for a few weeks, and the COVID-19 forecast hub does a good job of this. But when we get further than that, a lot of things can change that can fundamentally change the epidemiology of the COVID-19 pandemic. For instance, there could be new variants, as we well know now.

There could be substantial changes in policy or behavior. There could be different scientific uncertainty, the impacts of waning, for instance, that could substantially affect those long-term projections. But we still, as you all know, need to make plans on the sort of six-month to one year time scale. So, the

point of having these planning scenarios is to specify a long some critical axis what we're assuming in terms of some of those future events and then make projections under those assumptions to help with planning.

But fully recognizing that things will not unfold exactly how we expect, and these are not proper forecasts. And this is a complicated figure, but all you need to know here is two things. One is that lighter means better performance, and two is that the ensemble of models is on the left side of each of these graphs.

And why I'm showing this is to point out that though individual modeling teams may, in their scenario that most matched reality outperform the ensemble of all the models and given rounds, the ensemble is consistently one of the top performers, and it is one of the most consistent high performers. So, for that reason, I'm going to focus for most of what I say going forward on the summary of all the models captured in the ensemble that the scenario hub makes, not individual model results.

So, let's get into what round 13 was, what were our scenarios. So, we had two axes. Shown along the left here is an axis that reflected our scientific uncertainty having to do with immunological waning against infection -- symptomatic infection for COVID-19.

In our optimistic waning scenario, we have seen a slow immunological waning with about 50 percent of the population reaching the wane state after about ten months from infection or vaccination, and this partially mean state had a 40 percent reduction in protection from the baseline levels for symptomatic disease reported immediately after exposure with vaccination infection. So that's a 40 percent drop in protection -- a relative drop.

In our pessimistic waning scenario, we had fast immunologic waning, so 50 percent of the population were reaching the wane state within four months of either infection or vaccination, and this partially immune state had a 60 percent reduction in protection from baseline levels reported immediately after exposure. These scenarios are meant to be

somewhat bounding of the possibility.

Along the other axis, we captured one of the biggest sources of uncertainty in terms of how things might unfold -- and remember this is given what we knew in March -- with the left column showing no new variants so projections -- we're seeing the same mix of strains that was circulating around March and with the right-hand side assuming a new variant that started -- we started to see trickling into the United States with a continuous influx of introductions in this country around May 1st, 2022.

And this variant would have a 30 percent immune escape in the same intrinsic transmissibility and severity as Omicron. And though this variant was in no way based on BA.4 and 5, it is actually not fully dissimilar from what has actually occurred. But I would emphasize again that this was not an attempt to model those two strains specifically.

So, here are the resulting projections from the hub, and I'm going to dig in here into exactly how to interpret these in a moment. I would note that the bottom where we have the more pessimistic waning

assumptions and the right where we have the emergence of a new variant is where things tend to be tracking better with what we're actually seeing out there in terms of hospitalizations done in this dotted line. I'd also emphasize that these are weekly hospitalization numbers, not daily hospitalization numbers.

So, the way to read this figure is that we have what we're actually seeing, and then this darkest interval here represents a 50 percent projection interval. So, when we ensemble across the models we think there's a 50 percent chance that the weekly number of observed hospitalizations will stay within that range over the course of the period, and you see that that peaks out around 50 percent -- sorry, around 50,000 hospitalizations per week just top of that range.

In the next lighter shading is an 80 percent interval. We see that that goes and peaks out just under 100,000 hospitalizations per week, and that is peaking in the early fall. And then we have a 90 percent projection interval, so 90 percent probability

that we'll stay within this range that comes up into getting close to the 150,000 hospitalization per week range and then a 95 percent projection interval that tops out over 150,000 hospitalizations per week.

And you can see that the sort of probability of a peak is higher in the near-term from both waning and introduction of variant and in the fall time. So, when we're planning, we're really concerned, I think, often with our chances of being above some level. So, this is an alternate visualization that we've produced that really tries to capture that first heat map, and we note that the scale has changed here. It's still weekly hospitalizations, but the top of the scale changed.

So, the red part of this graph indicates an area where we're about a hundred percent chance we think we'll see more than this many hospitalizations in those areas. This beige area is sort of the 50/50. We think it's even odds that we'll be above or below that number, and then the dark blue is where we think there's almost no chance that we'll be. And just to give you a sense of where we are, the week of June 18th

we saw around 32,000 hospitalizations which was just over that 50/50 split point.

So, stepping back to look at the projections across everything, once again noting that we're tracking more with these pessimistic waning scenarios and that we do have some variants out there, of course, we see more -- or faster waning leads to higher likely case numbers -- hospitalization numbers, particularly in the nearer term, and particularly with the variant we see resurgences. In both cases we do see a substantial probability of resurgences in the fall.

This is looking at it in the other way, and essentially the information is the same with there being a fairly reasonable chance of substantial resurgences coming into the fall and winter months in addition to our more recent resurgence.

So, I just want to summarize some of the core messages here to close out. Incidence tracking with the more pessimistic scenarios, and that's scenario C&D in terms of waning at this point. Faster waning and new variants substantially increase expected hospitalizations. Variants lead to earlier resurgences

and bigger resurgences, and that's scenarios B&D. And under the most pessimistic scenarios, weekly hospitalizations are expected to remain under 170,000 per week and will likely stay between 13,000 and 52,000.

So, we have to caveat these results a bit. I would note that in this round in particular -- particularly compared to the Omicron round where there was a lot of agreement in the models and subtract quite well, we're seeing highly variable projections across the model.

So, you can see here looking in on this bottom right figure, that all the models are showing similar sized peaks for their most likely trajectory for hospitalizations, but the timing of those peaks differs substantially between the models. And I think that's reflecting a substantial amount of uncertainty in exactly how those trajectories unfold even if there is some consensus in terms of aggregate effect.

And since there isn't a consensus trajectory drawing a single line for the ensemble -- you notice we've avoided doing that -- it's difficult to do. And

these highly variable trajectories, we know that they are a result of a lot of sensitivity in terms of the projections through the baseline assumptions. And part of the reason we didn't know this, is that one team was good enough to present multiple models with only slight changes in the assumption about the way immunological waning looks.

So, what they did is they assumed it had about the same median speed of waning but a slightly different distribution, a sort of longer tail distribution versus the straight exponential decay, and even those small changes in waning can lead to substantial differences in exactly how their trajectories work. So, at the point where we were making these in March, I think we've seen more data and there's a bit less uncertainty now, but at the point we were making these projections in March, there was a lot of uncertainty. And small differences in assumptions can lead to big differences.

Hopefully, the goal of the ensembling and the using of multiple models is to capture a lot of those uncertainties and know the impact of a lot of those

written assumptions, so we, of course, are hopeful that the aggregate projections are still useful and informative for planning.

So, to sum up, between March 2022 and March 2023, we are expecting around 95,000 cumulative deaths to occur in the most optimistic scenarios. But as I said, it seems that we've definitely deviated from that, and we're probably in this most pessimistic scenario where we are looking at over 200,000 deaths occurring over that period with a 95 percent confidence interval of -- or projection interval, excuse me, of 52,000 to over 450,000. And I would note here that this is under current assumptions about vaccination policy and doesn't reflect the impact of any additional vaccine.

In the most pessimistic scenario, there's greater than five percent risk of exceeding the Delta hospitalization weeks in 10 of the 52 protection weeks, so in 20 percent of the weeks, and then more optimistic scenario is this is then true for (inaudible). There's lots of uncertainty in the precise trajectory of sensitivity to exact assumptions about waning and

protection against infection and new variants, of course, lead to larger (inaudible) peaks in most, but not all of them.

And to finally give some caveats, as I mentioned, there's substantial heterogeneity in projections between models and that reflects a scientific uncertainty that may be even greater than that captured by the ensemble. The main scenario axes represent things in which there's substantial underlying uncertainty. For instance, it is completely possible that we've see a new variant that is entirely different from anything that we tried to (inaudible) capture the model.

Four out of six national models included BA.2 and in some cases behavior change, and in three of these four showed resurgences in the April and May timeframe to commiserate with what we saw. Reported end cases and other metrics has been mentioned, undergoing significant changes and making it difficult to project those into the future. And while not only the model variants are not completely dissimilar from BA.4/5, they're in no way based on those variants, so

future rounds will be accounting more directly for what we have observed and for the epidemiology of those variants.

And with that, I'd like to thank the coordinating team and all of the teams that contributed models to both this round and previous rounds that are listed here. And for those who are interested in seeing -- digging in more deeply into these results, seeing state results and the like as well as future and past rounds, I direct you to the COVID-19 scenariomodelinghub.org website where all of that is available.

And with that I'm ready to take questions.

DR. ARNOLD MONTO: Thank you, Dr. Lessler. A point of clarification, I understand how your models project waning. The issue is how do you put intervals around emergence of new variants? For example, how well did the models predict what would happen if a very different variant, such as the Omicron, emerge again?

DR. JUSTIN LESSLER: So, we captured that in terms of defining variant in the scenario. So, we didn't attempt to capture all of the different possible

variants that could happen. We just modeled this single variant with 30 percent immune escape and otherwise similar to Omicron. So, the nature of new variances can have a very, very large effect on what we actually see as we all well know at this point. So, attempting to -- or not defining that in the scenarios and trying to integrate out across a ton of different variants would lead to massive, massive uncertainty.

So, we recognize that we may see a variant that is more like Omicron with something like 80 percent immune escape and maybe some transmission advantages, and in that case, we would see far bigger resurgence than anything projected by the model.

DR. ARNOLD MONTO: And how much did the emergence of Omicron cause you to rethink some of the assumptions that you've been using?

DR. JUSTIN LESSLER: It's certainly taught us that variants that are very different could have pretty -- were possible. I think that more extreme immune escape than we previously had been putting into our models was possible and then also I think indicated that there -- in terms of the impact on infection

versus the impact on severe disease -- that there can be pretty big differences in how much escape you have in infection versus severe disease, and we've done our best to capture that as we're thinking about new variants.

I will say, as a little bit of a point of pride, that we did a very good job of projecting the Omicron wave back in December, maybe better than we deserved to. But I think it was --

DR. ARNOLD MONTO: Was this after it emerged or before?

DR. JUSTIN LASSLER: It was when we had data from South Africa but hadn't seen anything --

DR. ARNOLD MONTO: You already knew how different it was.

DR. JUSTIN LASSLER: Yeah. We already knew how different it was, right. I think this gets into the planning scenario side of the whole thing, right. We don't pretend that we can say what a new variant will look like, right? We don't pretend that. So, we try to pick some scenarios that balance some reasonable possibilities, but we don't capture everything. And

it's more when something does come on the scene that substantially changes what might happen, like Omicron, we convene everybody for an emergency round to get stuff out as quickly as possible to put in that new information, and that's how we've responded so far.

Delta sort of -- we completely underestimated how bad Delta was going to be. But Omicron, based on early information from South Africa we were able to, I think, do a pretty good job of capturing exactly what the impact of that would be once we had that early data on its epidemiology. But we didn't have a crystal ball and (inaudible).

DR. ARNOLD MONTO: That's the problem because we're being asked more or less to have a crystal ball today. Dr. Levy.

DR. OFER LEVY: Hi. Thank you for that presentation. Very interesting. So as these different models are being put together, critical to the models are their underlying assumptions, the variables they take into account and the weight you ascribe to each of these variables, and you describe various different models that have different performances.

So, across time, are you measuring the performance of each model and then going back and changing the weight and the number of variables taken into account in order to further optimize the model? In other words, is the entire effort a self-learning effort that you try to continuously improve the overall predictive power of these models?

DR. JUSTIN LESSLER: Yeah, so I think it's important to separate out when thinking about that question the individual modeling teams versus the hub and the aggregation itself. So, the individual modeling teams are all constantly refitting their models. They're constantly learning from new data. They're constantly reweighting things. They're constantly adding or sometimes removing complexity from their model that allows them to both better fit the past trajectories and better capture what we're defining from the central hub and the scenarios into the future.

So, all of the models are going under a constant update and learning process, and I know from experience that even one or two weeks of data sometimes

can like -- the models can improve substantially from that and really take that into account. So that learning process is ongoing for the individual model.

What we're not doing is we're not -- at the hub level where we aggregate we're not weighting the models based on their performance in past rounds. Part of that is it's hard to -- unlike for a forecast where you are being asked to just say this is what's going to happen in the next couple weeks so there's a clear assessment of right or wrong, these are scenarios where we've defined a set of conditions for many, many months into the future that almost by definition are not going to happen exactly. So, figuring out how to best judge models in this that context is difficult.

Second -- and I'll also make a third point too -- second is that when we looked at it there's really a lot of variability in which model performed best at different times, and so there wouldn't necessarily be waiting on the last round would not necessarily give you benefit in that.

And then third, we use this ensembling method called linear opinion pools that really captures the

uncertainty in the models and the full breadth of uncertainty coming out of the model, and we found for this task over the course of it, that this linear opinion pool method would outweigh -- we just trim out some of the extremes that otherwise don't weight -- has been very good at consistently providing decent projections -- decent planning scenario projections.

With the caveat, as mentioned before, when a new variant comes along, it invalidates everything if we didn't have that variant in it. I hope that helps.

DR. ARNOLD MONTO: Okay. Thank you. And thank you, Dr. Lessler. I think we have no more questions. I do have a question for Mike. Can we start a few minutes early since we have a break coming up, or are we locked --

MR. MICHAEL KAWCZYNSKI: Yes we can.

DR. ARNOLD MONTO: -- into an 11:00?

MR. MICHAEL KAWCZYNSKI: No. Yes we can. That'll give us some extra time.

DR. ARNOLD MONTO: Right, why don't we reconvene at five minutes to 11:00 Eastern. So, we now have a 17-minute break.

MR. MICHAEL KAWCZYNSKI: Seventeen minutes, all right. I will set that timer. Here you go, and studio, if you could, take us to break.

[BREAK]

SPONSOR PRESENTATIONS ON CLINICAL DATA REGARDING VARIANT VACCINES

MR. MICHAEL KAWCZYNSKI: Okay. Good after- -- I guess we'll still say good morning. It depends on where you are. Welcome back to the 175th Vaccines and Related Biological Products Advisory Committee meeting. I'm going to hand it back to our chair, Dr. Monto.

DR. ARNOLD MONTO: Thanks, Mike. We now have three presentations from sponsors. After each of the sponsor presentation, we're going to have a short question-and-answer period. So, we are going to have to be very careful to keep the questions as focused as possible in order to keep on time because we have a very busy schedule up till lunchtime. So, first, Dr. Stephen Hoge, President of Moderna, will speak for that

company. Dr. Hoge?

SPONSOR PRESENTATION: MODERNA COVID-19 INVESTIGATIONAL BIVALENT VACCINE

DR. STEPHEN HOGE: Good morning. My name is Dr. Stephen Hoge. I'm the president of Moderna where I lead research and development. It's a privilege to present to the Committee today. The rationale for updating the vaccines has previously been covered, and the goals of variant-containing boosters include retaining neutralization for ancestral SARS-CoV-2, achieving stronger immune responses against current variants, broadening the cross-neutralization against future variants, and extending the durability of protection.

Over the last year, Moderna has evaluated three monovalent and three bivalent variant vaccine candidates. Our studies have included over 4,300 participants and evaluated two different dose levels. Today, we will focus on our bivalent vaccine candidates. Principally, we will discuss mRNA-

1273.214.

Our Omicron-containing bivalent vaccine, which includes 25 micrograms of our prototype vaccine and 25 micrograms of the Omicron variant. For additional context on our bivalent platform, we will also discuss mRNA-1273.211, our Beta-containing bivalent vaccine.

I'd like to briefly summarize the data that led us to pursue our bivalent platform. This comes from our earlier experience with the Beta monovalent and Beta-containing bivalent booster vaccines. Data showed that a booster dose of a monovalent Beta vaccine listed has lower neutralizing titers than a bivalent Beta-containing vaccine. This was seen at one and six months and against the ancestral virus and the Beta and Delta variants of concern.

Subsequently, a booster dose of the bivalent Beta-containing vaccine was compared to the authorized prototype booster. At both one month and six months, the bivalent vaccine elicited significantly higher neutralizing titers against ancestral virus and the Beta, Delta, and Omicron variants of concern. The titers were also more durable for the bivalent vaccine.

We evaluated both 50 and 100 microgram dose levels for both the prototype booster and the bivalent Beta vaccine. The 50-microgram dose level met all immune bridging criteria and was dose sparing and is now the currently authorized booster dose.

Today, we will focus on our most recent bivalent booster, mRNA-1273.214. This Omicron-containing bivalent vaccine has been administered to 437 participants in our ongoing Phase 2/3 study. These data add to our significant experience with the bivalent platform, including our prior experience with the Beta-containing bivalent vaccine for which we have a median follow-up of 245 days in 300 participants. We've also studied our prototype vaccine as either a third or fourth dose and used it as a comparator for the bivalent vaccine.

Study 205 evaluated our bivalent Omicron-containing vaccine against pre-specified objectives aligned with regulatory guidelines. These included superiority of GMTs against the variant of concern, non-inferiority of response rates against the variant, and non-inferiority of GMTs and response rates against

the ancestral virus. Type 1 error was well-controlled using a pre-specified sequential testing strategy.

Demographics and baseline characteristics between the study groups were consistent. Of note, the mean age was 57 and 40 percent of participants were over the age of 65 in both groups. Also, the median time between the second and third dose was eight months, and the interval between the third dose and the fourth dose administered in this study was four-and-a-half months.

Next, let's compare the safety and reactogenicity of the bivalent Omicron-containing vaccine, the authorized booster, and the second dose in the primary series. First, the local reactions. Our bivalent Omicron-containing booster is in the dark blue. The third dose of our prototype booster is in the middle, and Dose 2 of the primary series is in light blue on the left. The local reactogenicity profile was broadly consistent with the authorized vaccine. Most reactions were Grade 1 or Grade 2.

Similarly, the systemic reactogenicity profile of the bivalent booster was also consistent with the

authorized booster and most events were Grade 1 or Grade 2.

Turning to immunogenicity. The bivalent Omicron-containing booster elicited significantly higher neutralizing titers against Omicron than the prototype booster in a validated BA.1 assay. The bivalent Omicron-containing booster is again shown in dark blue and the prototype in light blue. Titers are shown for all participants on the left, those who had no evidence of prior infection in the middle, and those who had a prior infection on the right.

The bivalent booster led to higher titers in those with and without prior infection. As pre-specified in the protocol, and as per regulatory guidance, we tested for superiority of neutralizing titers against Omicron BA.1. The GMT ratio comparing neutralizing titers or the bivalent Omicron-containing vaccine versus the prototype was 1.75 with a lower confidence bound of 1.49.

Therefore, the success criteria were met demonstrating superiority in neutralizing titers. Both seroresponse rates were near 100 percent, meeting the

pre-specified non-inferiority criteria.

We also evaluated the performance of the bivalent vaccine against the ancestral virus. Here, we observed significantly higher neutralizing titers for the bivalent vaccine. The GMT ratio is 1.22 and the lower bound of the confidence interval excluded 1. Seroresponse rates were both 100 percent and non-inferiority was met.

Importantly, we also looked at the performance of the bivalent vaccine across age groups. We saw robust neutralizing titers against the ancestral virus and the Omicron BA.1 strain in both younger adults and those adults over the age of 65.

Binding antibody titers were also tested in validated assays against all prior variants of concern, including Alpha, Beta, Delta, and Gamma. The bivalent Omicron-containing vaccine demonstrated significantly higher titers than prototype as evidenced by GMR point estimates greater than one with lower bound confidence intervals excluding one for all variants tested.

So in summary, our investigational bivalent Omicron-containing vaccine, mRNA-1273.214 met all pre-

specified primary and key secondary objectives consistent with regulatory guidance. The study also showed that the safety and tolerability profile of the bivalent vaccine was consistent with the currently authorized mRNA-1273 booster.

Next, I'd like to discuss how our bivalent Omicron-containing vaccine can address the emerging variants. The predominant strain of the SARS-CoV-2 virus that we face in the United States has changed repeatedly during different periods of the COVID-19 pandemic. The emergence of the Omicron variant of concern earlier this year was a significant departure in the trajectory of the pandemic, resulting in the largest wave of daily new cases in the United States today.

The recommended booster dose of our prototype vaccine resulted in neutralizing titers against Omicron BA.1 of 629. With a fourth dose of the bivalent Omicron-containing booster, we've significantly improved upon that. Now reaching titers of 2,372, demonstrating the progress we've made against the Omicron BA.1 strain.

The challenge that we face is that the virus has continued to evolve, and BA.1 is no longer the primary variant of concern in the United States. As presented by the CDC, BA.1 has largely been replaced, first, by BA.2 and more recently by BA.4 and BA.5 subvariants of Omicron. This pattern of evolution is likely to continue.

So it's important that we evaluate the neutralizing activity of the bivalent Omicron-containing vaccine against BA.4 and BA.5 that are likely to be the dominant strains in the near future. While there are no currently validated assays against BA.4, BA.5, thanks to our collaborators at the Montefiori lab at Duke University, we have neutralizing assay data using the same protocols as our validated assays.

As expected from the prior literature, we see an approximately three-fold decrease in BA.4/BA.5 neutralization relative to BA.1. Nonetheless, as highlighted in red, the observed GMTs remain robust at 727 for those without prior infection and over 2,000 for those with a history of prior infection. Geometric

mean fold rises in neutralizing titers for BA.4 and BA.5 were significant -- more than six-fold for those with no prior infection and more than three-fold among those with prior infection.

The fourth dose of the bivalent Omicron-containing booster increased the BA.4 and BA.5 neutralizing titers to a similar titer regardless of age. For those over the age of 65 without prior infection, neutralizing titers reached 817. The six-fold rise in titers was consistent with what's observed in younger adults. As we saw in our prior results, the neutralizing titers were higher in those with prior infection. The fold rises were consistent by age -- three-fold in both age groups.

Neutralizing antibody titers have been used to infer vaccine effectiveness including for the authorization of the prototype booster and immune bridging to pediatric population. On the left, we see the neutralizing antibody titers of 828 against Delta and 629 against Omicron after a third dose of the prototype vaccine, which has been associated with real-world effectiveness against both of those variants.

On the right, in dark blue, the neutralizing antibody titers against BA.4 and BA.5 were comparable at 727 one month after the fourth dose of the bivalent Omicron-containing booster.

Summarized on this slide are published real-world effectiveness data from our collaborative study with Kaiser Permanente, which established that a booster dose of a prototype vaccine improved vaccine effectiveness against infection for both Delta and Omicron. The booster dose also improved effectiveness against hospitalization due to Omicron.

Finally, I'd like to summarize our upcoming data and plans for the 1273.214 bivalent booster. Additional data collection is ongoing. This includes immunogenicity for the BA.4 and B.A5 subvariants after the fourth dose of the authorized prototype booster, which will provide a comparator for the bivalent vaccine.

We're assessing the durability of immune responses with the bivalent booster at three and six months. The bivalent vaccine is also being evaluated in infants and children as a primary series and as a

booster. We will continue safety follow-up of all recipients.

So, in summary, our bivalent booster has the potential, we believe, to provide improved protection against COVID-19 in anticipation of a surge of cases this coming fall. We met pre-specified primary and key secondary objectives including superior neutralizing titers against Omicron BA.1 and significantly higher titers against the ancestral strain with a favorable safety and tolerability profile.

We also demonstrated significantly higher binding antibodies against the prior variants of concern, Alpha, Beta, Gamma, and Delta, and robust neutralizing titers against BA.4 and BA.5, including among adults over the age of 65. We've previously demonstrated a more durable antibody response with our bivalent platform. Based on these data, we will be completing our regulatory submissions within the next two weeks. Pending authorization, a large-scale supply of the bivalent Omicron-containing vaccine could be available in late July and early August.

Now, finally, I'd like to thank our study

collaborators, investigators, and most importantly, all of the participants in these trials. Again, I'd like to thank this Committee for the privilege of presenting with you today. We'd be happy to answer any of your questions.

Q&A SESSION

DR. ARNOLD MONTO: Thank you, Dr. Hoge. Would you please remind us which subvariant is included in your vaccine?

DR. STEPHEN HOGE: The current (inaudible) --

MR. MICHAEL KAWCZYNSKI: Hold on one second. Hold on one second. Moderna, can you turn down your room volume? We're getting a lot of -- we're hearing us back through your speakers. All right. Go ahead. We're good. Thank you. Go ahead, Arnold.

DR. ARNOLD MONTO: I was asking whether we could have clarification of the subvariant included in the booster of the Omicron subvariant. Is it BA.1? Thank you.

DR. STEPHEN HOGE: BA.1.

DR. ARNOLD MONTO: Right. Dr. Gans followed by Dr. Levy.

DR. HAYLEY ALTMAN-GANS: Thank you so much for that presentation and for the work that you're doing around this. I had a question about the bivalent, which has the 25 micrograms of the ancestral, and yet, that seemed to boost people's antibodies to that particular ancestral strain higher than the 50, and I wondered if you had any thoughts on that. That's my first question.

My second question is, I see you are testing this in children who are obviously naïve. So, you have the naïve comparator. Are you doing those same in adults because we are considering as we move forward what would be the best primary series for those individuals who haven't actually been vaccinated yet outside of the children?

My third one is, you noted that you're going to have three-month and six-month follow-up. However, these will probably hopefully be annual boosters, so we're wondering about the one-year follow-up, or I am. Thank you.

DR. STEPHEN HOGE: Great. Thank you very much for those questions. I'll start with the question about the performance of the bivalent platform as opposed to monovalent, in particular against ancestral strain. If I may call up slide AA2 while I do this. So we have evaluated three monovalent and three bivalent varied adapted vaccines over the last year and a half. The totality of clinical data has actually been very consistent with the findings in our 214 study that I just presented.

We started that work first with a Beta variant of concern, which was in early 2021 of concern globally. At the time, we tested our prototype booster, mRNA-1273 and saw the booster could increase neutralized titers to robust levels. Then we subsequently tested a monovalent Beta-containing booster, and we were able to achieve against the Beta variant concerns slightly higher level.

But what was remarkable is when we combined those in a bivalent, what we saw on the far right-hand side here in dark blue, with our Beta-containing bivalent was that we actually achieved similar levels

at one month of neutralizing titers, but extended durability of those titers, as you can see here, and only three-fold decrease as opposed to eight-fold decrease. So, the overall GMRs that we were seeing were about 0.9 at one month, but 2.3 subsequently.

Now, we subsequently took that forward -- and if I could see Slide IM-15 -- into a powered Phase 2/3 study to evaluate the performance of the bivalent vaccine platform against the authorized prototype. Again, that's to be consistent with regulatory guidance. Again, in this study, we looked at the ancestral SARS-CoV-2 variant of concern virus as well as the Beta variant of concern. As you can see, the GMRs here actually were above one.

The point estimate for one month was 1.28 for the bivalent Beta based booster compared to the prototype vaccine. So, actually, again, outperformed against the ancestral virus even though the prototype vaccine is matched to the ancestral virus. Most intriguingly, what we saw in this large study was an expansion of that difference GMR rose out to one after six months. By day 181, that GMR reached 1.69.

So, not surprisingly, we saw a similar picture, I guess, given what we see against ancestral, the Beta variant of concern, the Beta-containing bivalent saw all higher neutralizing titers at one month and an even more dramatic expansion in the GMR, geometric mean ratio, to 2.74 at six months.

So, what we've seen is a fairly consistent picture. When we use the bivalent vaccine platform, we are seeing higher neutralizing titers and that includes when we compare against monovalent prototype, which was not part of the question, but the same is seen here with a 211 bivalent and when we compare against a monovalent variant of concern, which I presented just a minute ago.

So, it's a consistent feature of the platform. We do think it has to do with presenting more antigenic diversity and perhaps other features of the molecular biology of what's been forward. We're working to answer those questions in months ahead. Now, quickly, to answer your second and third questions, in certain situations --

DR. ARNOLD MONTO: Very quickly. We're

running out of time.

DR. STEPHEN HOGE: Of course. In terms of testing seronegative adults, we will endeavor to do that if possible, but as many of us know, there are very few populations with seronegative adults. So, at this time, we are not conducting such a study, but if it becomes necessary to do so, we will absolutely. We are, as you mentioned, evaluating seronegative children where those populations exist.

And the third question in terms of 6-month and 12-month follow-up, we are, per protocol, evaluating through six months, but many of these participants are in our long-term follow-up in studies, and we will generate data in 12 months if possible.

DR. ARNOLD MONTO: Thank you. We're really getting into a time crunch. I would like to ask those on the Committee and the sponsors to keep your questions and answers very short. We're only going to be able to have two more questions right now. Dr. Levy followed by Dr. Offit.

MR. MICHAEL KAWCZYNSKI: Dr. Levy --

DR. ARNOLD MONTO: We can't hear you.

MR. MICHAEL KAWCZYNSKI: -- you have your own phone muted. You have your own phone muted.

DR. OFER LEVY: Oh, yes. Sorry. My question is two-fold. One is regarding immunogenicity, did you look at --

DR. ARNOLD MONTO: Only one-part questions from now on. Go ahead, Ofer. I'm sorry.

DR. OFER LEVY: -- did you look at T cell responses and (audio skip 02:43:18) efficacy? Thank you.

DR. STEPHEN HOGE: I apologize. It broke up. I didn't hear the question.

DR. ARNOLD MONTO: You were breaking up.

DR. OFER LEVY: Did you look at the T cell responses for immunogenicity and was there any evidence of clinical efficacy?

DR. STEPHEN HOGE: So, we've collected PDMCs sampled baseline at one month. We're going to do so again at three months. Once we have all of those samples collected, we'll be testing to look at some of these immunities. So, it is a part of our plan to do so. We haven't done that yet.

DR. ARNOLD MONTO: Thank you. Thanks for the brief answer. Dr. Offit?

DR. PAUL OFFIT: Yes. Thank you. So, maybe I missed this, but regarding the neutralizing activity against BA.4/BA.5, what, if any, was a fold increase of neutralizing antibodies when you boost it with the Omicron-containing bivalent as compared to just boosting with the ancestral strain. Was there a fold difference with neutralizing antibodies against BA.4/BA.5 with Omicron bivalent as compared to just the ancestral strain? I didn't see those data.

DR. STEPHEN HOGE: So, as I have mentioned, we are still collecting that data for the BA.4/BA.5 assay. So, we're specifically testing the performance of the prototype vaccine. We'll have that data very shortly. The geometric fold rises in just the Omicron-containing bivalents were six-fold.

We do have data comparing the geometric rises, the rises that you're asking for, Dr. Offit, across all of the other variants of concern including the Omicron BA.1 assay, the validated assay, and there, we did see a difference, and that's the basis of the statistical

superiority that we demonstrated. It is consistent. Between our BA.4/BA.5 assay and the BA.1 assay, we've generally seen about a three-fold drop in those neutralizing titers. So, we'll have that data shortly, but we do not expect there to be a difference in the performance.

DR. PAUL OFFIT: Because that's the critical question. I mean, it could get as Dr. Scobie showed with, say, the third or fourth dose of these ancestral traits, you do get some maturational infinity that includes these variants. So, you have to show clearly that your bivalent vaccine is significantly better than that. That's the critical question. Thank you.

DR. ARNOLD MONTO: Thank you. I agree. Dr. Chatterjee, we'll squeeze you in.

DR. ARCHANA CHATTERJEE: Thank you very much. I'll ask my question very quickly. That is, you mentioned that there are pediatric studies looking at the bivalent vaccines. Can you tell us what the time frame is within which we would receive results or we would be able to see results of those vaccines?

DR. STEPHEN HOGE: We've amended those

protocols now, and are underway. We would expect to have data assuming -- for the primary series, and so we'll give two doses, the second dose at one month and then follow for a month or two. So, we would expect to have that data in the middle of the fall.

DR. ARCHANA CHATTERJEE: Thank you.

DR. ARNOLD MONTO: Thank you. Thank you, Dr. Hoge. Stick around for the afternoon. We may have some questions that come up, but we're really locked in in terms of the schedule right now. Dr. Kena Swanson speaks next, Vice President of Viral Vaccines at Pfizer. Dr. Swanson?

SPONSOR PRESENTATION: COVID-19 OMICRON-MODIFIED VACCINE OPTIONS

DR. KENA SWANSON: Good morning. My name is Kena Swanson, and I am head of Viral Vaccines, R&D at Pfizer. On behalf of Pfizer and BioNTech, it is my pleasure to share both immunogenicity and safety data in support of an EUA for Omicron variant-modified vaccines to address the surge in COVID-19 cases. Based

on the fast pace of the SARS-CoV-2 epidemiology and need to roll out variant-modified vaccines, I will also propose options for future variant vaccine updates based on preclinical data and existing clinical data.

The SARS-CoV-2 variant epidemiology continues to change rapidly. You will notice on the left of the slide, since the beginning of 2021, we have seen major waves of variants of concern that emerged quickly, became dominant, then were superseded by the next VOC. With the emergence of Omicron in November of 2021, shown in the yellow box, we are today faced with a variant and its sublineages, which are the most antigenically distinct compared to prior VOCs, are more transmissible, and show evidence of partial immune escape from existing vaccines.

While the current prototype vaccine BNT162b2 administered as a two-dose series has shown robust neutralization against most variants to date. Going from left to right beginning with the reference strain in gray, neutralization titers against Omicron, the original BA.1 shown here in red on the far right are much reduced. However, after a third dose

neutralization titers against Omicron are substantially increased.

This graph shows plaque reduction neutralization titers after two doses presented on the left and three doses presented on the right for both the wild-type reference strain shown in gray and Omicron BA.1 shown in blue. This increase in Omicron neutralization titers has generally correlated well with improved protection against symptomatic COVID-19.

Real-world data demonstrate that vaccine effectiveness against COVID-19 is lower and wanes faster for Omicron compared to Delta, which corresponds with the observed lower Omicron neutralization activity.

The figure on the right shows the vaccine effectiveness against symptomatic COVID-19 after two doses of BNT162b2 shown on the top and of a booster dose shown on the bottom as reported by the U.K. Health Security Agency. Vaccine efficacy for Omicron, represented by gray circles, is lower at all time points compared to Delta represented by the black squares.

Although current vaccines have been effective at preventing severe Omicron illness in the general population, waning against Omicron-related hospitalizations has been observed at more than nine months after the second dose, and, with the third dose, duration of protection beyond six months is unknown. Given the burden of Omicron and the healthcare system and society and the erosion of protection of current vaccines against Omicron over time, it may be time to consider an update to the current vaccine.

Shown here, the clinical study in 18- to 55-year-olds designed to evaluate an Omicron-modified vaccine. The study compares a fourth dose booster of a monovalent Omicron modified vaccine to a fourth dose booster of BNT162b2, and it evaluates the monovalent Omicron modified vaccine in naïve individuals as a two-dose series.

The fourth dose was administered at a median of 3.9 months following dose three of BNT162b2. To meet the two primary EUA criteria of geometric mean ratio and seroresponse, superiority and an Omicron BA.1 neutralization assay was to be established between

Omicron modified and prototype vaccine groups based on the GMRs. Non-inferiority of the seroresponse was also to be established with seroresponse defined as achieving a greater than or equal to four-fold rise from baseline.

A descriptive analysis for the reference strain requires a comparison of the geometric mean neutralizing titers or GMTs between variant vaccine and prototype vaccine. In this study, for participants without evidence of infection up to one month after the fourth dose, data from a validated Omicron BA.1 SARS-CoV-2 neutralization assay demonstrate that both the GMR and seroresponse success criteria were met. Shown on the left with the GMR of 1.75 and lower bound of 1.39, superiority was met.

Moving to the right, a seroresponse difference of 23 percent between the Omicron vaccine group and prototype vaccine group with a lower bound of 11.1, showing non-inferiority was met.

The required descriptive analysis against the reference strain shown in this table is based on data from a validated recombinant SARS-CoV-2 reference

strain neutralization assay. Shown from left to right are the GMTs, the geometric mean fold rise, from one-month post-Dose 4 to pre-Dose 4. On the far right, the GMR, between the Omicron modified vaccine and BNT162b2.

Collectively, the data show comparable GMTs and satisfy the descriptive analysis, showing substantial increases in reference strain neutralizing titers for both vaccines when given as a fourth dose booster.

Next, we evaluated responses in naïve individuals following a two-dose series of the monovalent Omicron vaccine given three weeks apart. Data shown here are from a sentinel group of naïve individuals one month following immunization with two doses of the monovalent Omicron vaccine. From left to right are neutralization responses to the reference strain in gray, Delta in green, and Omicron BA.1 in blue.

In contrast to booster responses and those without vaccine experienced a primary series in naïve individuals elicits a predominantly Omicron-specific neutralizing response as shown here in blue. Responses

to the reference strain or Delta were limited. We also evaluated Omicron-modified vaccines in adults 56 years and older.

In this larger clinical study, we evaluated a fourth dose booster with either monovalent or bivalent Omicron-modified vaccines at two-dose levels, 30 micrograms and 60 micrograms. Dose 4 was administered a median of 6.3 months following Dose 3 of BNT162b2.

Again, stringent success criteria had to be met for GMR and seroresponse comparing variant vaccines to the prototype BNT162b2 at 30 microgram. Data shown here are Omicron BA.1 neutralization responses from each of the vaccine groups shown on the far left with the indicated N per groups and respective GMTs. As shown within the boxed area, the GMRs for each Omicron modified vaccine, both monovalent and bivalent align with the simple superiority criteria.

Furthermore, the monovalent Omicron vaccine at both 30 and 60 microgram dose levels achieved a lower bound 95 percent confidence interval for the GMR of greater than 1.5, consistent with requirements for super superiority.

This table is represented in the same orientation as the prior slide, but now showing the seroresponse for each group. Again, focusing on the boxed area to the right for the seroresponse difference between each variant vaccine compared to the prototype. Most important are the 95 percent confidence intervals indicated in each parentheses, which all maintained a lower bound of greater than minus five, consistent with requirements for non-inferiority of the seroresponse.

In addition to the formal analysis of the Omicron neutralizing response, shown here is the geometric mean fold rise or GMSR from one month after the fourth dose compared to the pre-Dose 4. High GMSRs were observed in all groups. Starting from left, with the monovalent vaccine GMSR ranging from 13 to 19.6 and moving to the right, a GMSR of 9 to 10.9 was observed for the bivalent groups. In total, these data illustrate the substantial increases in Omicron neutralizing antibody response with Omicron-modified vaccines.

Finally, a descriptive analysis for reference strain neutralizing titers from a sentinel cohort are

shown here using a SARS-CoV-2 fluorescent focused reduction neutralization assay. Each vaccine group is indicated above each column with GMTs before and one month after the fourth dose as well as the GMSR are listed in each row below. Descriptive analyses demonstrated increases in both variant vaccine and prototype vaccine groups.

The GMSRs were generally similar across the groups. As we have observed with prior clinical evaluation of mRNA variant vaccines, including Beta, Omicron-modified vaccines in participants 18 to 55 years of age showed a similar local reaction and systemic event profile as the prototype vaccine. In greater than 55-year-old participants, the Omicron-modified vaccines at 30 micrograms also showed a similar local reaction and systemic event profile as the prototype vaccine.

In those that received a 60-microgram dose level, mild to moderate injection site pain, fatigue, and muscle pain were slightly more common compared to the 30 microgram BNT162b2 group.

In summary, as we have shown, the responses

following a fourth dose booster of monovalent and bivalent Omicron-modified vaccines are consistent with regulatory criteria for simple superiority and, additionally, super superiority for the monovalent vaccine.

The reactogenicity profile of variant vaccines was overall similar to prototype BNT162b2 vaccine. EUA requirements were met for a vaccine update, and we can supply an Omicron-modified vaccine now. However, we are already faced with additional Omicron sublineages such as BA.4 and BA.5 that are rapidly expanding globally and may likely become the next dominant variant in the U.S.

Therefore, in a subset of participants in our older adult clinical study, we assessed neutralizing activity against the original Omicron BA.1 shown in dark blue and compared against neutralizing activity against Omicron B.A4, BA.5 shown in the light blue bars. BA.4/BA.5 contain the same spike sequence. The data show Omicron-modified vaccines neutralize Omicron BA.4 and BA.5 though to a lesser extent than BA.1. These data are consistent with published observations

following BA.1 breakthrough infection.

With the likelihood that Omicron BA.4 or BA.5 may become the dominant sublineage in the U.S., we need a more rapid mechanism other than clinical evaluation to enable availability of variant-modified vaccines in the U.S. to stem the health crises caused by emerging variants. Preclinical immunogenicity studies have reasonably predicted neutralization responses in humans in both vaccine-naïve and vaccine-experienced backgrounds.

For example, when the monovalent or bivalent Omicron modified vaccines were assessed in BNT162b2-experienced mice, we saw nearly identical trends as was observed in humans. Assessed from left to right are neutralizing responses against the reference strain shown in gray and Omicron BA.1 and BA.4/5 shown in dark and light blue. Overall, Omicron responses were higher in the Omicron vaccine groups both monovalent and bivalent compared to the prototype vaccine, and we saw reduced activity against BA.4/5.

These data suggest that going forward and based on the already extensive clinical experience with

variants-modified vaccines, which use the same mRNA platforms and are produced at the same process as the current vaccine, provision of preclinical immunogenicity data and an appropriate CMC data package could enable a more rapid response to the changing variant landscape.

If such a process were implemented, responses to future waves could be substantially accelerated. Vaccines that optimally match circulating strains could be better enabled both by the established body of clinical data and speed in which mRNA vaccines can be produced.

To conclude, EUA criteria were met for Omicron modified vaccines, both monovalent and bivalent. We proposed that an EUA be considered for an Omicron BA.1-modified vaccine to formally establish the pathway for variant-modified vaccines that would allow vaccine manufacturers in the future to provide variant-modified vaccines quickly with only CMC and preclinical data.

Now with the permission of the Committee, we would actually like to bring up a new slide that was provided to FDA this morning on late-breaking

preclinical immunogenicity data, evaluating both a monovalent and a bivalent BA.4/5 modified vaccine.

The data you're seeing on the present slide is pseudovirus neutralization titers in B2, BNT162b2 experienced mice that received a third booster dose with either the B2 prototype vaccine or a monovalent Omicron BA.4/5-modified vaccine in the middle in red and a bivalent BA.4/5 modified vaccine in purple on the right. What you can see is that there are substantial increases against all Omicron sublineages including BA.4/5 as well as the reference strain with the BA.4/5-modified vaccines.

So, we wanted to provide these data for this afternoon's discussion so that the Committee has all available data for those discussions. So, if we could just conclude, thank you for letting me share the new data. I would like to thank all the clinical trial participants, the sites, investigators, the CROs, our partners and their staff, and the FDA. Now my colleagues and I will be happy to take questions.

Q&A SESSION

DR. ARNOLD MONTO: Dr. Levy.

DR. OFER LEVY: Hi. Thank you for that. Obviously, in a difficult situation, quite quickly, and it's hard to generate sufficient information to know exactly what the right path is. So, regarding your miring data, you show the (audio skip) of neutralizing antibodies against BA.4 and 5. Were you able to challenge the mice to show that you had protection for the mice against clinical disease? Do you have an opinion as to what your correlative protection is in humans? Thirdly, have you made use of any human invitro models to assess your vaccines? Thank you.

DR. KENA SWANSON: Thank you, Dr. Levy, for the question. To answer the first, no, we have not challenged the mice. These data just became available this morning, so we wanted to share either the late-breaking of all of the totality of evidence that we have on variant-modified vaccines. So, these are to show the breadth of neutralization whether you're talking about a BA.1 modified or a BA.4 modified

vaccine compared to prototype. Then can you repeat the second question?

DR. OFER LEVY: (Audio skip) I mean, obviously, you have a lot of data now. What is your (audio skip) correlative protection is? Everybody's measuring antibodies, they're probably relevant, but as we know it's --

DR. ARNOLD MONTO: That's a long question. We need a quick answer.

DR. KENA SWANSON: I would say there is no established correlative of protection.

DR. ARNOLD MONTO: Thank you. That was a quick answer. Dr. Fink.

DR. DORAN FINK: Hi. Building on that last question about the mouse data. So, you showed a slide with a mouse experiment with the BA.1 component vaccine and then a slide of the late-breaking data with a mouse experiment with the BA.4/5 containing vaccines.

What we didn't see was any head-to-head comparison of neutralizing antibody titers elicited by the BA.1 component vaccine versus the BA.4/5 component vaccines. Do you have those data for head-to-head

comparison, or will you? Because that would really be helpful to help the Committee think about selection of various (inaudible) in the vaccines.

DR. KENA SWANSON: The preclinical data that was shown were two independent studies, and so we are generating additional data to have that side-by-side analysis of the BA.1- modified versus BA.4/5-modified vaccines. I think what you can see are consistent trends with the BA.4/5 modified vaccine either as monovalent or bivalent.

You are seeing superior Omicron neutralizing responses, particularly against BA.4, but also against the other sublineages compared to the prototype which is the control we're really trying to compare against in considering vaccine updates.

DR. DORAN FINK: Thank you.

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

DR. WAYNE MARASCO: Hi. Thank you for your presentation. I have a question. You may have shown it. There was a lot of data. I might've missed it. If you look at the bivalent vaccine, is there a relative difference in the fold increase in titers

between ancestral and BA.1? In other words, has there been some consumption so that the Delta that you could raise with the new variant is different than the ancestral variant during your boost?

So you're boosting with two different vaccines, ancestral and BA.1. My question is, the rise in titer from baseline, is it the same proportionally or different?

DR. KENA SWANSON: Let me just make sure I understand your question. So, are you asking what is the increase we see in reference strain neutralizing titers between the Omicron BA.1 monovalent versus bivalent?

DR. WAYNE MARASCO: Yeah. That's fine. You can answer it that way.

DR. KENA SWANSON: Okay. So, if we can -- we do have some slides that were presented in the core presentation, but for the sake of time, I'll try to be brief. So, we do see --

DR. ARNOLD MONTO: Yes. We don't need the slides.

DR. KENA SWANSON: -- similar increases --

DR. ARNOLD MONTO: Why don't you just -- just go ahead and answer without the slides if you can.

DR. KENA SWANSON: Sure. We see similar increases in the reference strain neutralizing titers between the prototype vaccine and the Omicron-modified vaccine. So, we show that both in the younger adults 18 to 55 with the Omicron monovalent, and then also we tested the monovalent and bivalent in the older adult study.

DR. WAYNE MARASCO: Thank you.

DR. ARNOLD MONTO: Thank you. We're going on now because of time constraints to the presentation by Dr. Gregory Glenn of Novavax. We'll hear about your research and development. Dr. Glenn.

SPONSOR PRESENTATION: NOVAVAX INC.

DR. GREGORY GLENN: Thank you very much. Good morning. My name is Gregory Glenn. I'm the president of Research and Development at Novavax, and I want to thank our colleagues at the FDA and the Committee members for inviting Novavax to provide input as you

consider vaccine coverage for future SARS-CoV-2 waves.

Today, I will discuss the structural features of our recombinant trimeric spike protein and present data demonstrating on how use of our vaccine results and broadly cross-neutralizing antibodies.

Because we extensively characterized our full-length spike protein, we have come to understand this vaccine construct displays conserved epitopes across prototype and emerging variants. Our adjuvant called Matrix-M promotes additional recognition of epitopes known as epitope spreading. This enhances recognition of conserved epitopes on the spike protein, which itself has a very high level of homology across variants, more than 97 percent. Together, these features induced antibodies that broadly recognize variant spike proteins.

Next, I'll present data on how our vaccine when given to previously immunized individuals or infected individuals induces broad recognition of variants following booster doses. I will then discuss the status of our ongoing clinical booster study and projected vaccine supply.

So, our vaccine contains recombinant protein in the form of a nanoparticle mixed with Matrix-M -- our adjuvant -- in a single vial and is stored and distributed at four degrees centigrade.

Our vaccine, NVX-2373, as based on the Wuhan strain, has been evaluated in two large, randomized placebo-controlled Phase 3 trials. The vaccine efficacy was consistent against mild, moderate, or severe disease in both trials and was 90 percent with 100 percent protection against severe disease.

These two trials were conducted when virus had begun to rapidly evolve. Yet, we observe consistent high levels of efficacy in the presence of a variety of variants. Additionally, as you can see, in the last row, we observed strong protection against any symptomatic or asymptomatic infection over six months. This suggests that the strength of protection is high and the Novavax vaccine may also help prevent transmission.

So, as you know, recombinant technology enables rapid production of spike protein through newly evolved viruses. Using electron microscopy, we can

visualize the high-resolution atomic structure of Novavax spike trimers. The Novavax vaccine is unique as it's a full-length trimer presented in a fashion that closely mimics the protein structure as found in nature and allows the immune system to recognize both receptor-binding domains and other portions of the spike.

On the right, you can see the nanoparticle with the detergent core, in which the full-length spike trimer is embedded. The detergent core acts like a membrane where the transmembrane domains these spikes sit, just as they do in nature. The ectodomain looks like an ice cream cone and lives outside the membrane. The receptor-binding domain is shown at the top, and we have colored in blue a known conserved epitopes, one present across all the variants shown here, which I think you'll see it's a familiar characteristic discussed earlier.

So, if you go to the next slide, we characterize the spike epitopes using monoclonal antibodies combined with electron microscopy. What we're looking at here, that pink is the binding of a

unique broadly monoclonal antibody derived from our vaccine that can neutralize all the viruses shown here.

We visualize this antibody binding to the spike, and this allows us to identify the location of binding at the neo acid level, and this confirms the presence of this conserved epitope shown in blue in the previous slide across the different variants that are shown here. It follows that, if we immunize any one of these spikes, we should induce this type of broadly neutralized antibody that recognizes this conserved epitope, which is present in multiple variant spikes.

This explains why, as we boost, we induce increasingly higher levels of antibodies that recognize variants despite the fact that the vaccine is based on the prototype Wuhan strain.

So, next, I'd like to review some key clinical evidence demonstrating the breadth of antibody responses to our vaccine in individuals who have been previously infected or received our vaccine. So displayed here are spike anti-IgG responses from our U.S. Phase 3 trial in individuals who receive the primary two-dose series and then a booster. The

horizontal dotted line indicates a level of IgG responses that approximate what was seen in our Phase 3 clinical trials and associated with high degrees of efficacy.

The binding series induces antibodies that recognize the prototype spike with lower levels of antibodies seen for BA.1, BA.2, and BA.5 spikes.

Now, a recent analysis from the Fred Hutchinson Cancer Center, the statistical group there, and the (inaudible) indicates that our anti-spike IgG correlates actually very well with protection from our vaccine. Thus, it's reasonable to presume that, based on this study, that the levels of Omicron-variant antibodies seen after priming could provide a good level of protection.

Now, the right panel represents antibody levels after a booster dose eight months after priming. This results in high levels of antibodies to the prototype to BA.1, BA.2, and BA.5 variants. The difference seen between BA.5 and prototype in the priming series, which is about 12-fold, decreases to only about four-fold after boosting.

But more importantly, the level of BA.5 antibody now approximates levels seen for our prototype in our Phase 3 studies, which again as a reminder, were associated with 90 percent efficacy.

So, here we present data from the same individuals using an assay that measures the ability of antibodies to block the binding of spike to the human H2 receptor, the first step in a human infection. In nature, this binding occurs with its very affinity and so only very affinity antibodies will block this interaction.

So, this assay is mechanistic, stringent, and detects antibodies that should prevent infection. It is also useful as reagents can be rapidly produced, helping us to promptly assess immunity to new variants. The responses measured to this assay also correlate well with microneutralization.

Now, on the left panel, we see that after the two-dose priming series, high level of antibodies that block binding to the prototype spike to the H2 receptor are observed.

When we look at this activity for variants,

the levels of these highly functional antibodies are low. However, after boosting at eight months, as shown on the right panel, we now see all the antibody titers are much higher and the levels reached against BA.1, BA.2, and BA.5 replicate levels we saw induced in our Phase 3 trial suggesting that we might expect similar efficacy now against the different strains.

So, this slide describes immunity from a small number of previously infected participants enrolled in our Phase 3 trial, and on the left, before immunization, it's clear that these previously infected individuals have negligible levels of receptor binding inhibition antibodies. This suggests these individuals would be susceptible to reinfection.

On the right, the same subjects, given a two-dose priming series of our prototype vaccine, exhibit a strong boost with high receptor binding inhibition responses to the homologous prototype strain but also strong responses to BA.1, BA.2, BA.5. The levels of BA.5 achieved approximate levels that were associated with protection and prevention of infection.

So in the Phase 2 study, we were able to study

the effects of two booster doses. Volunteers are given the vaccine in a two-dose priming series and boosted approximately six months later. In green, we see a strong boosting response to the spike IgG antibody response to the prototype strain. Note that this is displayed on a Log10 scale with titers well above the Phase 3 levels after this boost at six months. Now, six months after boosting the level remains high and, thus, durable and similar to what was achieved with our Phase 3 trial.

We then boosted again and observed further increases that we will track over the next six months. In this same figure, we've also plotted the immune response to Omicron BA.1 as shown in red. In these same subjects, we see both good boosting and importantly, a narrowing of the gap between the magnitude of the prototype responses and Omicron responses, which leads me to the next analysis.

So, here we see the same data in a multidimensional presentation of the immune responses called antigenic cartography, mapping our immune responses to multiple SARS-CoV-2 variants. This method

of analysis displays the antigenic distance between the antibodies arising for vaccination. Those recognizing prototype Wuhan strain in green and the relative difference in the magnitude of antibody recognition of the various relevant variant spike proteins.

Each square represents a two-fold or Log2 difference and, thus, three squares is an eight-fold difference. On the left panel, we show the antibody binding after a two-dose priming series. Here, the antigenic distances between Omicron subvariants are compared to earlier variants and are high. We annotated the distance between BA.5 in pink and Wuhan in green as this (inaudible) and has the most striking and clinically meaningful difference.

The middle panel displays responses after booster at six months. Now the antigenic distance has become smaller and between BA.5 -- the pink arrow -- and Wuhan has decreased from 9.9-fold to 4.2-fold.

On the right, after a fourth dose, the antigenic distances further decrease to a 2.1-fold and through the other strains is almost indistinguishable. It's, thus, reasonable to conclude from this analysis

that, as we immunize with additional doses over recombinant spike protein vaccine, we minimize the antigenic distance and begin to observe a more universal-like response against variants. We believe this response is driven by the recognition of conserved epitopes and further enhanced by the Matrix-M adjuvant.

Clearly, this fold or drift will be a key issue to be addressed with SARS-CoV-2 vaccines. Boosting with the Novavax prototype vaccine may be an option as it provides both high levels of antibodies recognizing variants and durable immune responses.

What I have described today recapitulates the past work we have done with our adjuvant or recombinant influenza vaccine where we showed clinically in three consecutive years that we covered forward drift with our H3N2 Matrix-M adjuvant vaccine as the virus actively evolved and escaped vaccine immunity.

So we have studied the Omicron vaccine in non-new primates. Animals were primed with our prototype vaccine and then boosted with either the prototype or Omicron BA.1 vaccine or a bivalent formulation. Each panel shows the immune response to boosting six months

after receiving the priming series with Wuhan.

On the left, we see a robust receptor inhibiting antibody responses to the BA.1, BA.2, and BA.5 variants after boosting with the prototype strain.

In the middle, when we used Omicron BA.1 vaccine as a boost, we observed better responses to BA.1, approximately 1.9-fold or better, as we would expect as this is a homologous antigen. Compared to the prototype immunization, no one (phonetic) has been a BA.5 response as observed. It's important to note that the BA.1 boosting also result in high levels of Wuhan-specific antibodies as shown in green.

On the right, we also boosted with a bivalent vaccine containing prototype, an Omicron BA.1. We see no advantages in any of the responses compared to boosting with BA.1 alone. Thus, while boosting with the prototype covers all the strains, providing an Omicron booster response enhanced immunity to the related subvariants. Taken together, we think that boosting with either the recombinant spike proteins with adjuvant may be an excellent option for covering the inevitable forward drift likely to arise with

future SARS-CoV-2 variants.

Finally, I want to briefly mention that we are conducting a study in humans to measure the effect of boosting in mRNA-primed subjects. This is a three-arm study including the 2373 Wuhan prototype vaccine, a monovalent BA.1 vaccine, and the bivalent prototype plus BA.1 vaccine, and we'll compare the immune responses to the variants along with trial arms.

So in summary, the Novavax 2373 vaccine has demonstrated a consistently high efficacy in two separate Phase 3 trials. Although the priming series induces antibodies that recognize the variants, boosting significantly enhances cross-reactive immunity, including the receptor-blocking antibodies in these forward-looking assessments. This phenomena, driven by the recognition of concerned epitopes, is due to the nature of our antigen -- a fully recombinant spike protein and the adjuvant, which both drive the breadth and duration of these immune responses.

Previously infected individuals who are a key target population for our vaccine mount impressive functional immunity to the priming series with our

vaccines. Heterologous boosting of mRNA primed subjects is being evaluated in the ongoing trial. Our nonhuman priming model which has served us well as a predictor of vaccine informants suggests no advantage for a bivalent vaccine but indicates that boosting with Omicron may better cover homologous strains. However, boosting with an adjuvant recombinant spike protein appears to be the most important strategy to cover newly emerging variants.

So with respect to future strain selection, we believe there continues to be a role for our recombinant protein vaccine based on the prototype strain. Our vaccine has been demonstrated to be efficacious against variants, induces broad immune responses against Omicron variants, and this may be the best choice for people who prefer a vaccine with an extensive safety and efficacy database.

However, we plan on having an Omicron-based vaccine available later this year based on the recommendation of this Committee or other health authorities. Our clinical study should be out in September, and we expect to have a very specific

vaccine if needed in quarter four of this year.

Thank you very much for your time and attention, and I would be happy to answer any questions.

Q&A SESSION

DR. ARNOLD MONTO: Thank you, Dr. Glenn. Dr. Gans, followed by Dr. Meissner.

DR. HAYLEY ALTMAN-GANS: Hi. Thank you so much for that, and I apologize for having missed the previous meeting where you presented.

I'm very intrigued by your boosting data. I had a question about that booster slide because it went by so quickly. I'm assuming that individual -- or maybe that was in the text, I'm not sure, but they had had the priming series was that the two doses of the prototype followed by either Omicron monovalent, bivalent, or just boosting with the prototype.

I'm curious that you say that there's no advantage to the bivalent, but it didn't appear actually to have a disadvantage in terms of what we

saw. So, I was curious about why you would move forward with a monovalent only in that case scenario.

DR. GREGORY GLENN: Well, I think that what you see -- I put the slide back up here -- is I think the conservation is driving these cross-reactant responses. So, with 97 percent conservation, you're essentially boosting Wuhan epitopes as well as Omicron BA.1 epitopes.

So, one thing we found early on in our development is that with five micrograms, we were at the peak response. In other words, we are at the top of the dose response currently. So, when they give five micrograms of our vaccine, we're peaking out at what's possible. So, when I look at this data, what I would say is, if you want to get closer to what might be circulating, that the variant vaccine could provide to the data. You can see that here, the Omicron BA.1 response is better, but really the bivalent's not adding anything to these immune responses. That's kind of what I would've predicted.

DR. ARNOLD MONTO: Dr. Meissner followed by Dr. Chatterjee.

DR. CODY MEISSNER: Thank you, Dr. Glenn, for that very interesting presentation. Two very quick questions. One, at the beginning, you suggested your vaccine may have some effect on mucosal immunity, and I wasn't sure if you were basing that on IGA concentrations or if you've actually looked at that or you were inferring it. Then number two, and I may have missed this, did you use your assay -- that is your H2 receptor binding inhibition assay?

Do you source the results of what happens in an individual who's infected by BA.4 or BA.5, the wild type -- those variants? Over.

DR. GREGORY GLENN: Yeah. Thank you. So just a little bit of aside. The reason we like that assay is it is an apples-to-apples assay. So the principle is we're blocking binding, which is very stringent. So, in infected individuals, this came from our Phase 3 trial. So, they were enrolled without a history of having previous infections, but then we were able to check their serologic conversion to end. These people turned out to actually have been infected.

So, we don't know how far out they were, how

far away from infection they were, but you can see that they offer almost no protection that would say block the first step in infection.

So why does this happen? So, the data I showed was looking at -- the data I showed and maybe we can go back to the efficacy slide -- is that we were able to show protection against both symptomatic and asymptomatic infection, again, using serologic criteria.

They seroconverted -- yeah, here we go. See at the bottom. So, this is actually a clinical follow-up of people for any symptomatic or asymptomatic disease based on serologic criteria. So, what I would say, we did -- in non-human primates, we have looked at this carefully, and it's quite readily detectible. You can see IgG and IgA in the mucosa of immunized primates.

When we challenge this finding here, the clinical finding is in concert with the finding we have in non-human primates where we really have sterilized immunity during challenge, and we've seen that with a number of challenge studies. So, it's clear, if there

is mucosal immunity, it's both IgG and IgA, and I think the clinical outcomes here show that the strength of the vaccine is very, very good.

DR. ARNOLD MONTO: Thank you. Final question from Dr. Hildreth. You're muted.

MR. MICHAEL KAWCZYNSKI: Sir, you have your phone -- yeah. You got your own phone.

DR. JAMES HILDRETH: I'm sorry. Dr. Glenn, can you hear me now?

DR. GREGORY GLENN: Yes.

DR. JAMES HILDRETH: Thank you. In Slide number 8 of your presentation, I want to make sure I understand this, that after an eight-month boost with your spike protein, you achieved antibody levels for BA.2 and BA.5 equivalent to what you found in your Phase 3 study; is that correct?

DR. GREGORY GLENN: That's correct. That's right. Yeah. You can see on the right that the other thing that happens is the -- so the gap between the prototype and the BA.5 diminish and then the level that you see is very similar to what we see in Phase 3. So, yes.

DR. JAMES HILDRETH: Very quickly. I --

DR. GREGORY GLENN: We see that with the more stringent assay as well. So, we're having immune responses, and it is a rather, I think, important breakthrough. I cited the paper by Peter Gilbert's group at the Fred Hutchinson that's done a wonderful job with collaborating with U.S. government on determining that spike IgG is a correlate for our vaccine.

It's actually quite dramatic in terms of the level of antibodies that are needed. I can maybe ask Dr. Mallory to briefly comment on it because I think it's such an important issue.

DR. ARNOLD MONTO: We don't have the time right now. Thank you.

DR. GREGORY GLENN: Okay.

DR. JAMES HILDRETH: Thank you, Dr. Glenn.

DR. GREGORY GLENN: Okay. Okay. Thank you.

DR. JAMES HILDRETH: Thank you.

DR. ARNOLD MONTO: Thank you. I'm very sorry to cut people off, but we have a very tight schedule before lunch.

WHO PRESENTATION: CONSIDERATIONS FOR VACCINE STRAIN COMPOSITION FROM THE WHO TAG-Co-VAC

DR. ARNOLD MONTO: Next, it's my pleasure to call on Kanta Subbarao from the WHO Collaborating Center in Melbourne, who will be telling us about considerations through vaccine strength, composition, and the WHO TAG-Co-VAC. Dr. Subbarao.

DR. KANTA SUBBARAO: Thank you very much. I hope you can hear me, Arnold.

DR. ARNOLD MONTO: We can. We don't see you yet.

DR. KANTA SUBBARAO: Yeah. All right.

DR. ARNOLD MONTO: But that's a --

DR. KANTA SUBBARAO: Hi.

DR. ARNOLD MONTO: That would be a pleasure, but that's a secondary consideration.

DR. KANTA SUBBARAO: Okay. There you go.

DR. ARNOLD MONTO: As long as we can see your Power- -- now we do.

DR. KANTA SUBBARAO: Okay. All right. So

thank you for this opportunity to talk to you about the deliberations of the WHO's TAG-Co-VAC Committee, and I'm going to move on here. So this is the Technical Advisory Group on COVID-19 Vaccine Composition. I've spoken to the VRBPAC before, talking through our deliberations at that point, but we've since released one more statement.

The functions of the TAG-Co-VAC specifically pertaining to this meeting are to recommend to the WHO for each COVID-19 vaccine platform adaptations, if any, are needed so that the vaccines continue to provide protection against variants of concern. So what I'm going to review today is the evidence base that we, as a Committee, that we reviewed, and I'm going to over some of the data that you've heard already from different presenters, but I'll just go over it so that you see what we reviewed.

We'll talk about the evolution of the virus and spread, vaccine effectiveness against Omicron, cross-neutralization and cross-protection data, following infection with the index virus or prior variant of concern or vaccination, antigenic

cartography that has been commented on already, and some of the preliminary data on Omicron infection, and preliminary data on candidate vaccines with updated compositions, although in the previous set of talks, you've probably heard something that was even more current than what I have.

So first, the evolution and spread. As all of you have seen before, these are images from Next strain showing from a year ago, the variants that have arisen, Alpha, Delta, Omicron, and now as you all heard, BA.2, I do believe, remains the dominant Omicron decedent but BA.4 and 5 are increasing in proportion.

So, this slide has a lot of information. So, I'm going to try to use my pointer, if I can do that. Hmm. I'm just going to -- no. It doesn't look like I'm able to -- oh, there we go. I can move that pointer now. All right. So, this is a busy slide, and so what we're talking about going from left to right are the vaccine effectiveness data from a number of different studies that are listed here, following primary vaccination series over a period of time from the vaccination.

On the right-hand side are following the boosters. Top to bottom is vaccination effectiveness against severe disease, against symptomatic disease, and all infection. So, what we see in vaccine effectiveness against Omicron that the index vaccines provide good protection against severe disease that is, in fact, boosted quite significantly with the booster. But the vaccine effectiveness against symptomatic disease and any infection are lower than the protection against severe disease.

Clearly, giving the booster does boost the protection against severe illness and hospitalization and disease.

So, in this paper from Walls and colleagues, I want to draw your attention, first to the left. So these are individuals that have had repeated exposures to SARS coronavirus 2, either through breakthrough infection through vaccination, post-infection, and so on. What's marked on the very bottom is a number of exposures that the person has had.

One, two, three, and there's a four in there. This is looking at the neutralization titers. Panel A

is looking at the neutralizing antibody titers against the index strain. Here, it's the G614D variant. You can see that with each exposure to the antigen, there is a boost in the neutralizing antibody responses. So, there is more following three doses than two doses, then one dose.

This follows through on the right panel when we're looking at the neutralizing antibody responses to Omicron. Again, you only see cross-reactive neutralizing antibody to the Omicron variant when the person's been exposed three or four times to the SARS-CoV-2 spike whether it's in the form of breakthrough infection or vaccination.

This is the paper that shows the responses to Omicron following one, two, or three doses of the Pfizer-BioNTech vaccine. You can see that you get a reasonable neutralizing antibody response to the Omicron variants BA.1 and BA.2 following three doses of the Pfizer vaccine compared to one and two doses. Again good neutralizing titers against the index strain in the Delta, but you really need a third dose to get a robust response to the Omicron variant.

Now, antigenic cartography has been commented on before. The circles represent the antigens. The squares represent the antisera, and each square represents a two-fold reduction. So, this is an antigenic map of the variants constructed from single exposure condolence sera, and you can see that the original virus and the early variants all cluster well together whereas the BA.1 Omicron variant is off by itself. BA.2 is somewhere in between.

On the right-hand panel is an aggregated antigenic map of the variants constructed using data from multiple sources. Here, you now see where BA.1 lies, and BA.2 and BA.4 is now shown on this cartography map. So BA.1 appears to be most antigenically distinct from the index virus than the other sublineages.

So, what happens when people have had Omicron infection? So, this is an important set of data. When you look on the left-hand side, these are people that have had Omicron infection, but they were previously unvaccinated. And so when people have had a BA.1 infection, they make a BA.1 response, some cross-

reactivity to BA.2, but really not much detectable neutralizing activity against the index virus Beta and Delta variants.

However, on the right panel, you see that when somebody has been previously vaccinated -- so they're previously primed -- and then have an Omicron infection, they have a cross-reactive response. You get a strong neutralizing antibody response to the Omicron strain that you've been infected with even if you were previously unprimed, but it isn't a broadly reactive antibody response. In a previously primed individual, you get good cross-reactivity.

These are data more recently from people that have had a BA.1 infection breakthrough infection in people that were either previously naïve in purple, and in green are those that were previously primed. So, previously unvaccinated individuals with a BA.1 breakthrough infection have a good response to BA.1 but less cross-reactivity to BA.4 and 5. Whereas, if they were previously vaccinated shown in green, you see a good response to BA.1, but you also have greater breadth of response to BA.4 and 5.

You're now looking at data on candidate vaccines with an updated composition. These are data from a mouse model looking at an Omicron-specific mRNA vaccine. So, the red Rs represent the Wuhan -- the index vaccine -- and the blue bars represent a BA.1 Omicron-specific vaccine.

So, when mice are immunized with the red immunogen, which is the index immunogen as an mRNA, they make a good response to the homologous vaccine, but they also make crossreactive-antibody against Beta and Delta but not against the Omicron variants. Whereas, if they're vaccinated with an Omicron-specific mRNA vaccine, they make a good response to the two Omicron strains but not to the index or the Beta or Delta variants.

In the same mouse model, now if you start with mice that have been primed with two doses of the mRNA-1273, which is the index-based vaccine, so mice that were previously vaccinated are then either -- those sera are tested directly. That is -- now I've lost my pointer. Hmm. All right. I've lost my pointer, so I'll -- oh, there we go. There it is again.

So, if we look at the brown bars, these are mice that have had two doses of the index mRNA vaccine. So they make a good response to the Wuhan index virus with less neutralizing activity to BA.1 and BA.2. Those mice, when they get a third dose, a booster dose, of the homologous index vaccine, they have a rise in titer against the index virus and a modest rise in titer against the Omicron strains. If mice instead after two doses of the index vaccine are given an Omicron boost, they have a robust response to the index virus and the most robust response of all of these strategies to the Omicron variants.

So, if we now look in a macaque study, this was a study done by the Vaccine Research Center at the NIH. On the left-hand side, you're looking at virus neutralization using a live virus neutralization assay and in the right panel is the lentiviral pseudovirus neutralization. The solid bars, these are macaques who had previously been vaccinated with two doses of the mRNA --

MR. MICHAEL KAWCZYNSKI: I don't see any at the moment. Let me see here.

DR. KANTA SUBBARAO: Oh, you're not seeing my slide.

MR. MICHAEL KAWCZYNSKI: I don't see any hands up.

DR. ARNOLD MONTO: I see the slide.

DR. KANTA SUBBARAO: Oh, you do see the slide. Okay. So, this is the macaque study in which macaques got two doses of the live virus of the mRNA-1273, and they were boosted either with the third dose of mRNA-1273 in the solid lines or with a Omicron specific booster in the dotted lines. At two weeks post-booster, the Omicron-specific vaccine, as well as the mRNA-1273 vaccine, gave similar neutralizing titers, and notably 70 to 80 percent of the B cells were cross-reactive against both index virus and the Omicron strain.

So, now moving on to data from clinical trials, this -- these are data that you've heard before directly from the manufacturers, but these are data from the use of a bivalent booster with the index virus and the Beta variant. What they show here, data in the blue are neutralizing antibody responses against the

index strain; in green, against the Beta variant; in magenta, against Omicron; and in orange, against Delta.

The first set of three data points are using the index-specific booster. The middle set are with an Omicron-specific booster, and what you're looking at here as the third dataset is at Day 180. What we see is that the bivalent vaccine that contains the index strain and the Beta variant provides similar titers of neutralizing antibody against the Beta variant but very notably have a longer longevity of that neutralizing antibody response at Day 180 compared to the index vaccine. We see this with the Omicron and the Delta variants as well.

So now, these are pre-booster and Day 29 post-boost titers in people that got an mRNA-1273 boost, which is a third dose of mRNA-1273 in the pale purple and a bivalent vaccine with both the index and the Omicron-specific vaccine. If you look at all participants seronegative or seropositive, we see that the bivalent vaccine induced higher titers against the Omicron-specific variant compared to the index. But there was also a very good response to the index virus

as well.

So, the evidence base, just to review and summarize, is, to date, Omicron is the most antigenically distinct of the variants of concern to have emerged with BA.1 appearing to be most distant from the index virus. Antibody responses in previously naïve, unprimed individuals exposed to Omicron are strong, but they are not broad.

They get a fairly high Omicron-specific neutralizing antibody titer, but limited cross-reactivity against other variants and the index virus indicating to us that a standalone Omicron-specific vaccine product will not suit the objectives of an updated COVID-19 vaccine composition.

Now, in contrast, in individuals who have been previously primed with SARS coronavirus 2 infection or COVID-19 vaccination with the index vaccine, a very broad immune response is elicited following Omicron infection. So, these data support a preference for the inclusion of Omicron and updated vaccine composition administered as a booster dose.

There are some limitations to the data that we

have at hand. There's a paucity of available data that we must acknowledge -- the minimal or limited data on cross-reactivity both in terms of breadth, humoral or cell-mediated immune responses in unvaccinated individuals or vaccinated individuals with breakthrough BA.2, BA.4, and BA.5 infection.

We have minimal or limited data on humoral and/or cell-mediated immune responses over time following Omicron infection in naïve individuals and those who have had breakthrough infection. Data are only available for the BA.1-specific updated vaccine response in naïve or primed animals; no data on other Omicron sublineage-specific vaccines were available or reviewed.

Limited data are available on immune responses using an Omicron BA.1-specific vaccine used as a booster in humans. Some of the data had just come out in the last week or two. All of the limited data that we had on variant-specific vaccine products in animal models and humans were using mRNA vaccines.

So I will now move on to the proposal from TAG-Co-VAC for updated vaccine composition. So, the

continued use of currently licensed vaccines based on the index virus confer high levels of protection against severe disease outcomes for all variants, including Omicron with a booster dose and is, therefore, appropriate to achieve the primary goals of COVID-19 vaccination which are to prevent severe illness and death.

But given the uncertainties of the trajectory of SARS-CoV-2 evolution and the characteristics of future variants, it may be prudent to pursue an additional objective of COVID-19 vaccination of achieving broader immunity against circulating and emerging variants while retaining protection against severe disease and death. I will point out here that our goal here is to achieve broader immunity against circulating and emerging variants, and it is not so much to match what is likely to circulate because there's so much uncertainty about the trajectory of this evolution.

The available data suggest that the inclusion of Omicron, as the most antigenically distinct variant of concern, as part of an updated vaccine composition

may be beneficial if it's administered as a booster dose to those who have already received a COVID-19 vaccination primary series.

We do not advise the use of an Omicron-specific monovalent vaccine product as a standalone formulation for the primary series because it's not yet known whether an Omicron-specific vaccine will offer the cross-reactive immunity and cross-protection from severe illness caused by other variants of concern in naïve individuals as the index vaccines have done so well.

For Omicron-specific vaccine products, the TAG-CO-VAC recognizes that viruses or viral genetic sequences very closely related to BA.1 are some of the most antigenically distant from the index virus to date and are likely to enhance the magnitude and breadth of the antibody response.

So, while we recommend an Omicron-containing vaccine product if people want to enhance the breadth of the immune response, our recommendation does not preclude consideration of other variant-specific formulations or bi or multivalent products by

regulatory authorities and that data support the fulfillment of the additional objective of achieving breadth of cross-reactive immunity to previous, currently circulating, and/or emerging variants.

I think that is my last slide. With that, I'll stop and see if you have any questions.

Q&A SESSION

DR. ARNOLD MONTO: Thank you very much, Kanta. I know that twice a year, you go through trying to take limited data on new variants and make specific recommendations. If you had to, as an individual, not as a member of a TAG, make a recommendation on which subvariant of the Omicron to include -- because we have to take one of them, and we have to take it soon -- which would you pick based on the antigenic cartography and the risk?

DR. KANTA SUBBARAO: So reiterating that we can maintain good protection from severe illness and death with an additional booster dose of the index vaccine, I still think there's value in increasing the

breadth of immunity. I will reiterate that we're not trying to match what may circulate. We're trying to increase the breadth of the immune response without losing the benefit from the index vaccine that's performed so well.

So I would choose the antigenic variant that is furthest out, and that would be BA.1 at this point. We simply don't have enough information on any of the other variants, but I could make a strong case based on our experience with influenza that using a virus to boost that is antigenically as far as possible is a better strategy than something that is part way there.

DR. ARNOLD MONTO: Simply because you can't predict?

DR. KANTA SUBBARAO: Yes. We can't predict at this point, and I can't --

DR. ARNOLD MONTO: Besides the breadth?

DR. KANTA SUBBARAO: Yes, but the breadth is important.

DR. ARNOLD MONTO: Okay. Thank you very much. Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Yeah. Dr. Subbarao,

I was curious about data in pediatric populations. Most of the data we've seen today has been from adult populations. Did the TAG group look at any pediatric data, and could you share any information on that with us?

DR. KANTA SUBBARAO: No. Unfortunately, we did not see any data beyond what I presented as the evidence base. I think this is very much a committee that's going to be active and continue to look at data as it emerges.

So far, I think, as a generalization, I'd say that the data that we've seen in children does mimic what we see in adults. So, I don't see any red flags in the data that we've seen so far. But having said that, I haven't seen Omicron-specific data in children.

DR. ARCHANA CHATTERJEE: Thank you.

DR. ARNOLD MONTO: Dr. Perlman followed by Dr. Reingold.

DR. STANLEY PERLMAN: Hi, Kanta. So, I have one question for you. From the WHO perspective, the recommendations that you're suggesting may be useful for vaccine manufacturers that have nimble facilities

to change their vaccine. How do you view this in terms of the many other vaccines worldwide that may not have the same kind of capabilities, or do they all have the same capabilities to formulate vaccines according to your recommendations?

DR. KANTA SUBBARAO: I think that's a really important point is something the committee really struggled with because, unlike VRBPAC that is specifically meeting about a recommendation for the United States, the WHO is really looking at what would work globally. The recommendation that we're making on strain composition will apply to all the currently licensed vaccines.

So, we don't have a full sense of what the capabilities for the different formulations or different platforms are, but I mean, I just want to reiterate that if companies do not change, then I do believe that the booster doses of the index vaccine have continued to provide good protection. So, it's more the added advantage of breadth that you would get from an updated composition.

We don't want the world to lose confidence in

vaccines that are currently available because we do know and data has been presented already that they do perform well in achieving the primary goal of immunization.

DR. ARNOLD MONTO: Thank you. Dr. Reingold followed by Dr. Offit.

DR. ARTHUR REINGOLD: Hi, thanks for that presentation. So, this is a simple-minded question, and maybe everyone else knows the answer, but is the implication of your recommendations that we really need two different vaccines? One for an initial series in people who are unvaccinated and one as a booster? Or can we get by with just the bivalent vaccine for everybody whether it's their first series or whether they're being boosted? Thanks.

DR. KANTA SUBBARAO: No. That is a question that we've thought about. At this point, the main thing that we felt was that a standalone monovalent Omicron vaccine would cause some concern because it may not provide the breadth of immunity in an unprimed individual. So, it's possible that a bivalent product might achieve that, but I think it would be important

for regulators and manufacturers and, you know, the field to see the response to both the Omicron strain as well as cross-reactive immunity with the bivalent product.

In the absence of that, I mean, our main point was that the data from infection and immunization with an Omicron infection or Omicron vaccine is that it provides good immune responses to Omicron but not the breadth. In primed individuals, we get both.

That's why at this point, it looks to me or the committee basically said that in a previously primed individual, an Omicron-specific booster would be great, but, if somebody is not previously primed, they should be primed with the index vaccine before being given a monovalent Omicron booster. A bivalent product might be able to meet both of those, but we'd have to see the data.

DR. ARTHUR REINGOLD: Thank you.

DR. ARNOLD MONTO: Okay. Thank you. Dr. Offit followed by Dr. Gans.

DR. PAUL OFFIT: Thank you for that presentation. I'm trying to put together some of the

ways that you've worded this. So, on the one hand, you state correctly and clearly that with the current ancestral strain vaccine that you get with additional doses beyond Dose 2, a broadening immune response and that these vaccines have held up regarding protection against serious illness. Then you're also trying to make the point that with Omicron, which is clearly a strain that has crossed the line in terms of immune invasiveness, that, by adding that, you get a broader response, which you are arguing will be clinically relevant and will be longer lived. Nonetheless, in your conclusion, you used the term "may". In other words, that by adding Omicron, this "may" be of value. So, I just felt that you played it sort of halfway there, but your comments.

DR. KANTA SUBBARAO: Right. The statement is written by committee and what we didn't -- the reason for the word "may" is that all of the data that we have is based on immunogenicity. So, it's extrapolating from that greater breadth of immune response and greater antibody risk antibody titers that we anticipate that that will translate into greater

effectiveness, but we don't have those data. Hence, the "may".

DR. PAUL OFFIT: Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Gans followed by a final question from Dr. Berger.

DR. HAYLEY ALTMAN-GANS: Thank you so much for this data. I really love, actually, your data and the way that you've actually expressed it. I had a question since the WHO maybe has the availability to look at this outside of these particular pharmacy strategies which are obviously just using their product and the idea of mix and match, which might be a more real-world experience. We had some evidence here and some guidelines that we can do that with some of our boosting but a question on that sort of more globally as things come into fruition.

Just the way that you express the bigger breadth of immunity, I think it's so important because there's been a lot of comments about this antigenic anchoring and these exposures. And I think that's really important with your data, and the data that's out there. And there's also some T cell data about the

epitopes being broadened also. I think that's an important concept, and I love that you have brought that out. I just want your thoughts on that specifically. So thank you for this and those two questions.

DR. KANTA SUBBARAO: Sure. So, I think the first one is easier for me to answer because the implementation of vaccines is really under the bailiwick of SAGE. SAGE released a statement alongside the TAG-Co-VAC statement. So, our committee, the TAG-Co-VAC was very specifically addressing composition, not how it would be used. So, I'd refer you to the SAGE statement and they will -- as products that come available, they will address how best to use them.

I know that there are a number of studies going on that are supported by CPE (phonetic) and others to look at mix and match to see how best to use what's available and enhance the protection as best as we can. I'm not sure I caught exactly what your question was in the second part about breadth.

DR. ARNOLD MONTO: We're going to have to move on. So, please stay available later on because we may

be able to come back to some of these questions which are a little away from some of the main points we need to come to some conclusions about today. Dr. Berger, final question. One part, please.

DR. ADAM BERGER: Thank you so much, Dr. Subbarao, for that presentation today about what the WHO has put together. I think this is somewhat of a simple question, but I'm just wondering because the data you presented was all based on mRNA vaccines being administered. I'm wondering if you evaluated the differences between platforms with those that are protein-based and whether the recommendations that WHO is putting forward. There were more specific to mRNA vaccines than any other types of vaccines that might be available.

DR. KANTA SUBBARAO: So I think I tried to point out in the limitation slide that the only data we had to look at were based on the mRNA platform. So we did not have data from other platforms. We'd welcome any additional data and will continue to look at that and provide additional updates in the future.

DR. ARNOLD MONTO: Thank you, Kanta. You've

really moved us along. Thank you. Next, we'll hear from Jerry Weir, FDA, who will all give us the assessment of the available data and talk about what we are going to be doing after lunch and the open public hearing. Dr. Weir.

FDA PRESENTATION: FDA ASSESSMENT OF AVAILABLE DATA FOR MODIFIED COVID-19 VACCINE CANDIDATES AND CONSIDERATION OF POTENTIAL CHANGES TO COVID-19 VACCINE STRAIN COMPOSITION

DR. JERRY WEIR: Thank you. We've got -- a little short on time. By being the last speaker of the morning, a lot of what I will say has already been covered, and I think that will allow me, hopefully, to get through things pretty fast. Also, even though some of it will be redundant, it will be a recap that I think, hopefully, will be useful in leading us into the discussion that follows later today. So, to start off as an introduction, to show you basically where we are and how we got here.

At a previous meeting of the VRBPAC on April

6th, 2022, the Committee discussed the process that would be used to update the composition of COVID-19 vaccines in the U.S. and considerations for use of additional booster doses. The April 6th discussion was not intended to make a specific recommendation for vaccine composition, and there were no voting questions, but there was some general agreement on several key points, including some of the ones that I've listed on this slide.

One was that strain change decisions should be data-driven, and there should be evidence to indicate that a proposed modified vaccine composition would likely provide improved effectiveness compared to the current vaccine formulation. A second key point was that decisions on COVID-19 strain composition should be a coordinated process led by the FDA with VRBPAC input. The Committee, during their discussion, noted the challenges of global coordination, and this was just alluded to in the previous discussion.

There was general agreement that the VRBPAC should consider any global strain composition recommendations in its deliberations. The expectation

of the Committee was that the VRBPAC would meet again when additional data was available to consider whether and how SARS-CoV-2 strain composition of COVID-19 vaccines in the U.S. should be modified. So, that's why we're here today.

We'll go to the next slide. I've listed the considerations for modifying COVID-19 strain composition. So when considering a recommendation to modify the COVID-19 vaccine composition, several key questions will need to be addressed by the Agency and the VRBPAC. In a sense, these are general considerations, general questions that would need to be answered at any time we considered strain composition changes.

I'm going to read them. A couple of them will be easy, and a couple of them will be harder. The first one is, are there SARS-CoV-2 virus variants circulating that are antigenically distinct from the strain included in the current vaccine? Second, have currently circulating SARS-CoV-2 virus variants become, or are they expected to become, dominant and displace earlier virus strains?

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

So, we're going to walk through these one at a time. Again, the first two will be pretty easy. Are there SARS-CoV-2 virus variants circulating that are antigenically distinct from the strain included in the current vaccines? I'm showing you a quick phylogenetic tree. You've seen these before. This one was taken from the covariants.org website, and it used data from Nextstrain. I wanted to make a couple of points here. This is a simplified phylogenetic tree.

But the points are that, one, of the virus variants of concern during the two and a half years of this pandemic, the variants of concern have not evolved from each other. In other words, Beta didn't come from Alpha, Delta didn't come from Beta. Omicron, no one's sure quite where it came from, but it didn't come from

any of those other variants that have previously circulated. That's point number one.

The second point is that if you look in the middle of the slide where you see the Omicron in yellow and red, Omicron does continue to evolve as we already know, and it has also separated into what -- the top part's the BA.1 and the bottom part, the BA.2, which is now further evolved into BA.2.12.1 and BA.4.5. So this continues to evolve.

It's true that we don't know where the viruses will go from here. I think it's fair to say that the longer Omicron is the dominant and almost only virus circulating in the world. The odds improved that whatever comes after this will come from Omicron. It has been now six months, and there's no guarantee, but at least that's a realistic possibility.

This slide shows what others probably already know is the cumulative ammino acid changes in Omicron spike relative to the spike of prototype vaccines. This was, of course, the reason Omicron was so concerning when it first emerged was just the sheer number of changes, about approximately 35 depending on

which index strain you compare it to. The top line lists all the BA.1, the BA.2 changes that are common to BA.1 and BA.2, and the key take-home message, of course, is that so many of these changes are in the receptor-binding domain and the in-terminal domain where a lot of the neutralizing antibodies responses focus.

Below that, you see amino acid changes that are specific to BA.1 and also the ones that are specific to BA.2. Notably, if you look at the bottom, the 2.12.1, which has been circulating in the U.S., and the BA.4/5, which have been circulating in other parts of the world and are now circulating and increasing in number in the U.S., you see that the number of changes relative to BA.2 are not that many. So, in other words, they're very closely related to BA.2, but I'll emphasize that all of these Omicron sublineages are much more related to each other than they are to previously circulating strains.

Back to the only one or two, three or four changes in BA.4/5 relative to BA.2, I'll just remind you that it's not always the number of mutations that

matter. Sometimes it's actually what the mutations are as we know from the SARS-CoV-2 as well as influenza; sometimes one amino acid change can make a dramatic difference.

If we go to the second question, have currently circulating SARS-CoV-2 virus variants become, or are they expected to become, dominant and displace earlier strains? Again, you've seen this before and it's pretty straightforward.

This is a chart, again, from covariants.org showing the proportion of virus variants in the U.S. over time. Starting with the coding on the right shows with the green Delta, how Delta was replaced by BA.1, which was replaced by BA.2. And then in the U.S., 2.12.1, which is the dark blue, and is now becoming probably displaced by BA.4/5. The nice thing about this website is, of course, it's interactive and you can see what the relative numbers of ratios of the different variants at any time.

You can also pick any country in the world and do the same sort of analysis. If you took the same graph for South Africa, for example, you wouldn't even

see the BA.2.12.1. You would just how 4/5 is the dominant virus variant in that country.

The third question -- and now it gets harder as we go -- is there evidence that current vaccines are less effective against new circulating virus variants than against previous strains of the virus? Here, again, we start with the effect of mutations in Omicron S on antibody neutralization. As already mentioned, there are numerous mutations with spike protein, and these include key mutations in both the receptor-binding domain as well as the in-terminal domain.

I think someone in one of the earlier presentations mentions what I have on the second bullet. It was noticed very early after the emergence of Omicron the reduced neutralizing activity of approved and authorized therapeutic monoclonal antibodies against Omicron. While you can say this isn't necessarily a vaccine issue, it does highlight, though, the differences in the spike between Omicron and earlier strains and how it does affect the neutralizing antibody response.

There also have been quite a few studies that

have documented reduced neutralizing activity of vaccine sera against Omicron, and you've seen several examples of that already today.

This slide just shows another example. This one was from recently published work, and again, it's the same method you've already seen. In this case, there were neutralization titers and sera from 39 vaccinees, and the data shown is against D614G Delta and Omicron BA.1.

You see after two vaccinations you get notably lower titers against Omicron compared to the index strain; three vaccination improves that. Again, the titers against Omicron are notably lower than against the wild-type or the prototype strain.

Also, you've seen some evidence of this, and I think somebody quoted the same paper earlier today. That's evidence for the reduced effectiveness of current vaccines against Omicron variants.

Currently, available vaccines continue for the most part to be effective against severe disease outcomes caused by Omicron. The primary series vaccine efficacy against Omicron appears to be reduced, but

with a booster, it does seem to improve close to that of previous variants.

On the other hand, vaccine effectiveness against symptomatic COVID-19 due to Omicron is reduced, and this shows an example measuring symptomatic COVID-19 disease and infection after two doses of Moderna vaccine on the left and after three doses of the Moderna vaccine on the right. The overall effectiveness is improved after three doses, but, if you look at the red line, you see it's quite a bit lower than the same sort of vaccine effectiveness against Delta.

Moving on. The next question, is there evidence that a candidate vaccine with an updated strain composition will be more effective against new circulating virus variants and provide an improved clinical benefit? You've already heard from the sponsors, a couple of sponsors with candidate vaccines. In considering the current epidemiology of SARS-CoV-2, studies with candidate vaccines that include an Omicron component are relevant to inform a decision on vaccine strain composition.

Among COVID-19 vaccines currently authorized or approved for use in the U.S., clinical immunogenicity data for modified versions, including an Omicron only BA.1 component, are available for the Pfizer-BioNTech and Moderna COVID-19 vaccines.

The available immunogenicity data are limited to neutralizing antibody responses and mostly following a fourth or second booster dose. The data and analysis provided by the sponsors have come in recently. They have not been independently verified, and some of the data at least been derived from assays that have not completed validation. Nevertheless, they're important for considering strain composition decisions.

This slide is a single slide about the Moderna COVID-19 vaccine. You've heard this already today. The population with 18 years or older. They have basically compared a 15-microgram mRNA containing the prototype, which is their approved booster dose, against the bivalent containing 25 of the prototype and 25 micrograms of the BA.1 S protein -- encoding the BS1 [sic] protein.

Again, you saw this earlier, if you look at

the GMTs and the GMT ratio, you see in the bottom right, the GMT ratio of the modified bivalent vaccine is 1.75 compared over the prototype mRNA-1273.

If you look at the Pfizer-BioNTech data, this was from one study of previously uninfected adults 18 to 55, evaluating a 30-microgram mRNA encoding prototype S protein. This is their approved booster dose against a monovalent 30 microgram mRNA encoding Omicron BA.1 S. Again, if you focus on the bottom right, you see the GMT ratio of the modified vaccine, again, 30 micrograms compared to the prototype 30 microgram dose. Once again, the GMT ratio 1.75.

There was a second Pfizer-BioNTech vaccine study. This was in adults greater than 55 years of age and they evaluated several groups in this study. One, again, was a monovalent 30 microgram encoding the prototype S. They compared that to two different monovalent formulations, 30 and 60 micrograms of mRNA encoding the Omicron BA.1 S protein. And they compared two different formulations of bivalent candidate vaccines, one with 15 and 15 micrograms and one with 30 and 30 micrograms of prototype and candidate BA.1.

If you just look at the very bottom row here, which is the GMT ratios of each of the test groups compared to the control 30 micrograms of the prototype, you see GMT ratios of 2.23 for the comparable 30 microgram of the Omicron. You see actually a higher ratio with the 60-microgram dose at 3.15. When you look at the two bivalents, both are higher responses against Omicron: once again, the 30-microgram dose 1.56 and the higher dose 60 micrograms containing 30 micrograms of each component of 1.97.

So, this slide gives the summary of the key data from all of these studies as it relates to a strain composition decision. Again, I'd just remind you, we're not here evaluating these vaccines per se. We're trying to use their information to help guide a strain composition decision for all vaccines.

If we summarize, the clinical immunogenicity data from candidate modified vaccines contained in an Omicron BA.1 component -- and this, again, is all mRNA vaccines, but it is from two manufacturers -- the data indicate an improved statistically superior Omicron BA.1 neutralizing antibody GMT compared to the

prototype vaccine from each manufacturer for all candidate vaccines tested, and that includes both monovalent and bivalent candidate vaccines.

The ancestral strain neutralizing antibody response to the candidate modified vaccines did not appear to be decreased compared to the prototype vaccine.

In the one study that evaluated different doses of candidate modified vaccines, the Omicron BA.1 neutralizing antibody titer appeared to correlate with the dose of Omicron component in the vaccine, and that appeared to be true for both monovalent and bivalent formulations.

So taken together, the available data indicates the potential for improved vaccine effectiveness against the Omicron variant when an Omicron component is included in the vaccine.

So, this is the data that we have for candidate vaccines in humans. There are some limitations of these studies that, even though the data is very promising, that should be kept in mind when we evaluate this data. One is that there's a limited

number of vaccine formulations that can be evaluated in clinical trials making optimization of formulation. This goes back to decisions of monovalent, multivalent, as well as dose difficult.

Once again, as has already been brought up today, only neutralizing antibody is measured, and how relative differences in neutralizing antibody titer relate to clinical benefit is unknown. The available data are mainly limited to an evaluation of a second booster dose, and, at this time, the use of modified vaccines for a first booster dose and definitely for a primary series would need to rely on some sort of extrapolation. It may not be as reasonable to make that extrapolation for a primary series in vaccine-naïve individuals.

All of the Omicron-containing candidate vaccines evaluated to date have a BA.1 component, and the neutralizing antibody analysis is focused on the BA.1 virus sublineage. That was shown in the previous slides. As you heard from the manufacturers, there has been some recent updated data looking at the neutralizing antibody for other Omicron sublineages

that work is still ongoing.

I'll also remind you that the data for the durability of the neutralizing antibody response is limited and only right now available for one-month post-dose at the present time.

So, in addition to the human clinical immunogenicity data with candidate vaccines, we, just like the WHO, ask ourselves whether there is additional data, additional evidence to support the effectiveness of an updated vaccine composition as booster. There have been several studies that have shown that vaccinations followed by infection with a variant of concern leads to an enhanced and broad antibody response to SARS-CoV-2 variants of concern.

These results in total suggest that vaccination followed by a booster vaccination with a variant of concern might also lead to a broadened antibody response. Of course, infection's not the same as vaccination, so these results are all suggestive, but they do at least add to what we know, and they do sort of present an increasingly common picture.

So I actually have a couple of selected

examples from recently published and unpublished studies. These are in addition to what was just presented by the WHO, but I'll remind you even before I show the slides that these involve different methodologies, different subject populations, and assays. In most cases, assays are not validated and are standardized, and also, as may be obvious, the data have not been submitted to the FDA and the FDA has not made an actual determination about scientific or regulatory applicability. The next two slides show a little bit of additional data.

This slide, which was from a collaborative study of four principal investigators, two Pollett and Mitre from the Uniform Service University of Health Sciences, Katzelnick from NIH, and the Weiss lab at CBER, shows what happens after BA.1 infection of previously vaccinated individuals. What you see is a landscape analysis, and essentially, you're looking at the antibody titers to different antigens. All the antigens are listed on the left with a red box around the Omicron antigens.

Actually, if you look on the individual

panels, those Omicron antigens are sort of grouped to the left, and they're all some version of red. What you see is the antibody titers to those different sublineages are lower than compared to the antibody response to other antigens which group more to the right of the slide. On the other hand, what you see is after two doses of vaccine, you get a higher antibody response and greater breadth against Omicron variants than in the left panel with three vaccine doses.

Interestingly, you actually see a similar picture in the middle on the right panels where the effective breadth after BA.1 infection of two vaccine doses is actually somewhat similar to the same effect after three vaccine doses.

The next slide shows a somewhat similar picture. This was recently published just actually in print in the last week or so. Neutralizing antibody titers against Omicron subvariants following vaccination in BA.1 or BA.2 infection.

Here you see on the left panel before a booster and after a booster sera analyzed against Omicron several subvariants. You see once again,

before boosting, very, very low titers against all the Omicron sublineages. After booster, those titers go up. But again, as you've seen before, these are lower than against the ancestral strain, the Wuhan Washington strain, which is the highest.

On the other hand, in a limited group of patients who were both vaccinated and then infected with BA.1 or BA.2, you see an increased antibody titer to all of the Omicron sublineages. Again, when you look at them, even though they're quite a bit higher than after vaccination alone, you see, if you look at BA.4 and BA.5, these titers are still lower than, against BA.1, BA.2, as well as the original prototype strain from Washington.

Okay. So, summarize where we are, back to the considerations that will always have to be addressed, as I said, some of this is easy, and some of it is hard. But currently, circulating SARS-CoV-2 viruses are antigenically distinct from strains that circulated early in the pandemic and on which current COVID-19 vaccines are based.

The SARS-CoV-2 Omicron variant has become

dominant globally. It poses a higher risk of reinfection than previous SARS strains. I didn't show data for this, but this is published. It also continues to evolve into sublineages that are also antigenically distinct.

By several measures including escape from antibody neutralization and protection against infection, the current vaccines appear less effective against Omicron variants than against previous strains of virus. But taken together, the available data indicate that an Omicron booster vaccination will increase and broaden the antibody response to SARS-CoV-2 Omicron viruses.

So if we conclude and show the future directions, which I think is the last slide, again, to restate this, the preponderance of the data indicate an improved antibody response to SARS-CoV-2 Omicron variants and the potential for an improved vaccine effectiveness when an Omicron component is included in a vaccine booster. That being said, all of this is very promising.

That being said, there are many challenges in

the uncertainties that remain. One of which is vaccine formulation decisions, again, back to the dose, the monovalent versus multivalent. All of these will probably be important for the antibody response to a modified booster vaccine.

Vaccine effectiveness studies will be crucial in determining if higher and broader antibody responses to variants of concern actually translate into clinical benefit.

I'll also remind you that the protective antibody titers for highly transmissible viruses, such as the recent Omicron sublineages may be different from those protective antibody titers for previous strains.

Finally in the challenges, modification of the COVID-19 vaccine composition will include programmatic and operational challenges. We're all aware of that. We understand that this will be difficult, but I think for today, we focus on what we need, and then we will try after this to figure out how to meet the programmatic and operational challenges.

The last future direction I wanted to mention is the strain composition process for COVID-19 vaccines

will benefit from further refinement, and that includes improved coordination and consensus regarding the types of data needed for strain composition decisions, as well as where and how such data is generated.

I think we've made enormous progress in this whole endeavor over the last few months, but I will remind you that the sort of parallel track of influenza strain selection, which works very well, was a process that was honed over many, many years. So, we probably have quite a bit of work. This is a different virus. We have a lot of work to do in this strain selection process for COVID vaccines.

So, I will stop there. The next two slides have the discussion questions for the Committee, but these will be flashed up later when we get there. So, I think I can stop now. Back to you, Dr. Monto.

DR. ARNOLD MONTO: Great. I think because we have a hard stop for preparation for the oral public hearing, we're going to have to not only park the discussion topics but park any questions until after the lunch break and the oral public hearing. You can start us off at that point with the discussion topics,

and then we can have the question-and-answer sessions after we've seen the discussion topics.

DR. JERRY WEIR: That sounds great.

DR. ARNOLD MONTO: So, we'll break now until --

DR. PETER MARKS: Dr. Monto --

DR. ARNOLD MONTO: -- after 1:30.

DR. PETER MARKS: (inaudible) suggested that what we'll probably do is add a period. There are a number of responses to questions and answers that we'll just ask if we can, our sponsors, and anyone who can from this morning to stay around because I think there will be -- at the beginning of the period after the open public hearing -- kind of an opportunity where a number of questions could get answered at the beginning of that period. Thanks.

DR. ARNOLD MONTO: All right. We'll break now.

MR. MICHAEL KAWCZYNSKI: All right. So, with that, Dr. Monto, I will take us to break. We will reconvene in 30 minutes around 1:30. Studio, if you could kill the feed.

[BREAK]

OPEN PUBLIC HEARING

MR. MICHAEL KAWCZYNSKI: Just waiting. Okay. And welcome back from that lunch break. We are getting ready to kick off our OPH session. I'm going to hand it back to our chair, Dr. Monto, and Peter Marks, director. Take it away.

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the Committee of any financial relationships that you may have with the

sponsor, its products, and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of expenses in connection with your participation in this meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. Dr. Marks.

DR. PETER MARKS: Thanks very much, Dr. Monto. I just want to make just a brief statement here for people's benefit. You know, as Dr. Monto noted, FDA welcomes comments from all interested members of the public during the open public hearing portion of the Advisory Committee meeting. We welcome and respect input into the topics being discussed at today's meeting, but we don't in any way accept or condone comments that include offensive remarks or hate speech, particularly any remarks directed at members of the Advisory Committee or FDA staff. Thanks very much and we look forward to a productive open public hearing.

Thank you.

DR. ARNOLD MONTO: Over to Prabha.

DR. PRABHAKARA ATREYA: Thank you, Dr. Monto. Before I begin calling out the registered OPH speakers, I'd like to add the following guidance as well. FDA encourages participation from all public stakeholders in its decision making processes. Every Advisory Committee meeting does include an open public hearing session during which interested persons may present relevant information or their views.

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

With this additional guidance, I would like to conduct our open public hearing session by calling the registered OPH speakers. The first name is Dr. Dustin Bryce. He has a PowerPoint presentation. We have

several PowerPoint presentations, but some are also oral comments. And each one gets three minutes to make their point. Okay. Thank you and the first speaker is Dustin Bryce. You can start. You have three minutes.

MR. DUSTIN BRYCE: Hello. My name is Dustin Bryce, interestofjustice.org. I have no financial interested involved. This is a notice of claim of rights for revocation of the EUA and notice of error in approving mRNA for use in babies and healthy people.

FDA, CDC and the WHO are usurping the Congress definition of vaccine, which is "any substance designed for the prevention of one or more diseases." FDA actually classifies mRNA as gene therapy, which they say is to treat or cure an existing disease by modifying your genes. Gene therapies are still being studied and are marked experimental at this time. Next slide, please.

Gene therapy unlike a vaccine is so inherently unsafe the FDA says it should require 15 years of research to follow up on safety due to known risks of antibody dependent enhancement, altering your DNA, and delayed adverse effects up to 15 years later such as

cancers. Next slide, please. FDA says that gene therapy use in mass populations represents an unreasonable risk and they should limit the number of subjects who might be exposed to risk. We require due process and forbid the FDA from authorizing the proposed changes.

We are demanding the EUA is promptly results because unreasonable risks are inherent in gene therapy products as evidenced by large numbers of reports of adverse serious events linked to or suspected of being caused by the EUA product, product failure, product ineffectiveness. Next slide, please. The problem is EUA laws have only two prongs, one, to prevent infection, or, two, to treat an existing disease. At this time no mRNA product has ever been found to be effective for the prevention or prophylactics of infectious disease, only monocolonal antibodies. Rationally the EUA for mRNA products cannot be under the EUA prong to prevent infection.

The only other prong is that EUA can also be issued to treat an existing disease. Congress never authorized any use of investigational products outside

the clinical trials in healthy masses of people. It's illegal to give to healthy people mRNA at this time because FDA's EUA violates superior laws and other nations' regulatory provisions who rely on FDA to harmonize laws to meet FDA's international duties. Next slide, please.

Composition changes in the current product could easily be a bioweapon says Moderna. If you could change one line of code, it has profound impacts on everything. FDA says with gene therapy you have to extrapolate from the trials, and the trails show a failing deadly product that gave all animals ADE. Next slide, please.

The CDC and FDA, Pfizer-BioNTech phase IV date shows death is common. 1.1 percent died. If you take BioNTech that number seven effect after 30 days is death. Delayed reactions to mRNA are known by FDA, whose willful misconduct omits to inform the public of death in violation of superior law. Next slide, please.

Pfizer testified the FDA knows of Pfizer trial flaws. If FDA authorizes the changes with no trials,

is FDA in violation of international human rights obligations? Yes. We demand the EUA is promptly revoked and they're not expanded for the boosters to evade safety trials and data. Thank you so much for this time to speak. We do not want this to happen.

DR. PRABHAKARA ATREYA: Thank you. The next speaker is Michael Briskin. You have three minutes, please.

MR. MICHAEL BRISKIN: Hi, my name's Mike Briskin. I have no conflicts of interest, but I'd like to announce that roughly have the FDA's budget is funded by pharma and approaching three-quarters of its review budget. That sounds like a conflict of interest to me. Slide two, please.

I've heard the phrase "safe and effective" several thousand times over the last couple years, which is curious because it's not clear how you can call something safe with no long term testing, especially when that something is a pegylated pseudouridine modified nucleotide chain injection in a world where we don't understand epigenetic phenomena, we can't reliably predict protein misfolding. We

understudy the biodistribution effects on the vasculature, et cetera. Slide three, please.

And long term questions aside, in the short term 2021 was a very interesting year. We saw historic increases in deaths among working age adults, 18 to 64, and specifically in Q3 and into Q4. So something new for the working age demographic partly through 2021 would be the clear correlation. We have comparable trends in BLS data, German health insurance data, Israeli ambulance data. Slide 4, please.

And of course we have the VAERS data which the CDC tried to minimize but a recent FOA requested forced them to reveal that they never once did a PRR calculation that was supposed to be their tool for spotting safety signals according to their posted documents. Slide five. And what do we do when people get injured from these vaccines? We leave them in the mud. Slide six, please.

Two weeks ago this panel signed off on shots for toddlers. The Pfizer trial could not demonstrate efficacy after two shots and so gave a third, ignoring everything prior in the trial so they could put out a

press release of efficacy based on ten cases. Three-quarters of the severe COVID in the trial was in the vaccine arm, as was the only hospitalization case, which was accompanied by a seizure. If those eight or nine cases are too small a sample, then so is ten mild cases, and we have to admit that that drug was authorized based on no efficacy at all.

Neither trial had the statistical power to detect serious events, and Moderna is so dangerous in young people that other countries won't allow it for anyone under 30. In fact the director of health of Denmark just admitted that vaccinating children was a mistake, whereas our officials only ever doubled down. And now we're about to double down so hard that we lose even the pretense of holding these companies to any statistically meaningful regulatory standard for formula modifications.

For those trying to keep track at home what this agency is proposing is not just modifying the genetic code and the structure of the proteins produced to chase variants but even things like doubling the microgram count for Pfizer, all without doing any

statistically powered safety studies. Slide seven. And to be clear the companies we're giving carte blanche to include Pfizer, the world's largest criminal organization having paid the world's largest criminal fine, and Moderna which never made a safe product before we did away with long term safety testing and made prove more iniquitous still. Last slide, please.

This last slide is a review of ethics, primum non nocere, first do no harm. You may think that's antiquated, but the modern version of the Hippocratic oath out of Tufts says, "Above all, I will not play god." Perhaps you think the notion of god is archaic. You haven't read the CTME, and you think that human subsystems of reality are smarter than the systemization as a hole. Okay.

Then let's just go with a cautionary principle which is that novel technology requires more testing, not less. You're violating every possible ethical principle that could be applied. The only shame is in doubling down. Please stand up for scientific integrity and pump the brakes. I know you can do it, and to leave off I have one question for the panel.

DR. PRABHAKARA ATREYA: Your time is up, please.

MR. MICHAEL BRISKIN: What would it take to not authorize? That is the question, and if you can't answer that, let's scrap the FDA.

DR. PRABHAKARA ATREYA: Your time is up, so wrap it up, please. The next speaker is Eric Feintuch.

MR. ERIC FEINTUCH: (Inaudible).

DR. PRABHAKARA ATREYA: We can't hear you well.

MR. MICHAEL KAWCZYNSKI: Prabha, I'm gonna skip Eric, and we'll come back to him. Eric, I will reconnect your audio. Let's go to the next one. We'll go to Brucha, and Eric, I will call you back in.

MS. BRUCHA WEISBERGER: Hello (Inaudible). My name is Brucha Weisberger, and I do have a major conflict of interest with the FDA because I work for god. I like seeing everyone stay alive and healthy. Apparently there's no longer any use in talking to the FDA, so I appeal directly to god and to the people to open their eyes. All the fraud we see here has been foretold in Psalms, and the one above is directing the

show. (Inaudible).

Today we witnessed the death of science at the FDA. They've been captured by the multibillion dollar pharma industry to the point of total corruption. There's no fear of god, but he's orchestrating their downfall. He caused them to become reckless and obvious about their lack of science as they approve new shots without any evidence that they work.

That's what happened with the children's authorization. 4,500 kids were in the trial, but 3,000 dropped out. Why? And the efficacy after the first shot and after the second shot, many more kids in the vaccine group got COVID than in the placebo group. The shots harmed kids and caused infection, but they don't count that data. They ignore 97 percent of the COVID cases in the trial, and they cherry pick only the COVID case count after three shots. Their entire claim of efficacy is based on a difference of four children. Is this science?

That's what the FDA will do again today. They'll approve new shots with added variance based only on antibody levels that the shots simulated in the

blood stream. That's the new fake science that they call immunobridging. As we saw in the kids' trials, it doesn't work in real life.

To add to the comedy they'll be approving shots for variants that don't exist anymore. Coronaviruses mutate so fast that a vaccine can't keep up with them, and the vaccine actually drives mutations. So nothing makes sense here. This total death of science seems horrible, but it may cause people to finally wake up and realize that the FDA's a laughingstock and must be disbanded for the safety of America. (Inaudible).

These slides will give a glimpse of the hundreds of thousands disabled and killed by the COVID shot. I know many of such people personally. Since there isn't enough time to do justice to the many grave issues such as male and female infertility, I ask the public to go to my site, truth613.subsect.com, to learn more. Slide two, please.

The CDC and FDA didn't tell us, but we know from other sources about a doubling of the miscarriage rate and a doubling of the newborn death rate after the

vax rollout. Slide three. Numerous locals are showing a drop in birth on a scale which is impossible to happen by chance, and it only started after the vax. Taiwan had a 23 percent drop in births in the first quarter of 2022. This is a sterilizing vaccine. Slide six, please.

A 25 percent increase in cardiac arrests linked to these vaccines, and the FDA's still not recalling them. Something is rotten. UK data shows that all cause mortality rate is up to six times higher among COVID vaxxed individuals compared to unvaxxed, so how does this shot save lives when it is increasing death? Slide eight. Dr. Peter Shirmacher, chief pathologist of the University of Heidelberg, was threatened with the death of his family if he continued to speak about the results of his autopsies showing that 30 to 40 percent of the people he checked had died from the vaccine. Slide 15.

Why does FDA continue to kill people by saying that the old safe medications don't work for COVID when the doctors who prescribe them are saving tens of thousands of patients with barely a single death? And

then the FDA expects us to trust them? Slide 17. Why won't Dr. Peter Marks debate Dr. Peter McCullough or any of the doctors who warn about the great dangers of the COVID shots? Slide 18. We reached an all-time low in our country as open scientific discussion to arrive at the truth has been squashed, punished, and shut down. The FDA has a choice. It can either stand up --

DR. PRABHAKARA ATREYA: Your time is up.

MS. BRUCHA WEISBERGER: I'm finishing -- and recall the killer COVID shots which bring nothing but death and destruction, or it will soon fall into oblivion and disrupt because of its grave negligence and uselessness in protecting the people. Thank you.

MR. MICHAEL KAWCZYNSKI: And Prabha, I do have Eric back on.

DR. PRABHAKARA ATREYA: Okay.

DR. ERIC FEINTUCH: Okay. Hi.

DR. PRABHAKARA ATREYA: Yeah. Go ahead, Eric.

DR. ERIC FEINTUCH: Okay. This is Dr. Eric Feintuch of the Unalienable Rights Alliance, Picture Perfect Health. I'm a doctor of chiropractic. Let's go to slide two. I wanted to explain to you --

everyone knows about the spike protein, but let's just discuss it briefly.

The mRNA -- how long does it stay in the body? Can anyone answer how long it stays in the body? How long does it continue to produce the spike protein? Can anyone answer that? What is the rate of protein production? What's a consequence of this methylpseudouridine substitution about staying and getting into the blood-brain barrier?

What about the fact that we humanized it and we made it so that it can go anywhere it wants? Is there anyone here on this panel would say that it doesn't go everywhere? Tell me what proof you have of that. Slide three. The multinucleated cell which shows cancer is coming up, and here's the PubMed research on it. Slide four. We need to know that we don't have a reemergence of cancer. We need to know whether the spike protein does that. Number five.

How can you assure us that the mRNA doesn't cause Parkinson's? Here's information about the bodies like pathology in vitro. Slide six. Luc Montagnier, he did a *Preprint* paper before he passed away. Twenty-

six people were presented to him. Three people within like two months of taking the second mRNA shot, all of them are dead now. Unfortunately, Luc passed on, but he was the Nobel Prize winner for HIV. And his information needs to be researched and seen. Slide eight -- let's go to seven and then go to eight, please.

Eight is how the spike protein works, why it creates a H2 and ace inhibitor issue and why we have myocarditis. Are we going to double down -- go to nine. Are we going to double down in our future framework that basically does not allow us to research and see whether or not clinical studies need to be done by just saying it's immunobridged? Is this the new math? We urgently need to create a correlated projection equation that doesn't just include neutralizing antibodies.

You noticed that even people on the board were saying this may happen, or they are not so sure that it is not on the fourth or fifth variant. Well, guess what? The production to produce this takes months and look how fast the variants are changing. So as it

changes, our production abilities are not even going to catch up to three or six months.

These have to be addressed. You're not prepared to actually treat this properly. Nevertheless, you're calling it a vaccine. It's really a gene therapy, as addressed by earlier speakers. Go to number ten.

This idea of what we increase risk to infection is all about our G quadruplexes, the exosomes and microRNAs. I want every one of you gentlemen to read these peer reviewed articles. Let's go all the way to the end. All right? Number 17, please.

A thousand peer reviewed studies question the COVID-19 vaccine safety, a thousand. They graduated from Harvard, Yale, Stanford, every major university. They probably graduated with you, everyone that's on this board. I have a lot of faith in you. I see you working hard. Doesn't any see the safety signals? Is there anyone here that will stand up? I know it'll be hard to go to work tomorrow, but thalidomide, they say it was approved in Germany, Canada, and in the UK. And as someone who was born in Canada which created the FDA

eventually said no, there's a safety seal. Please listen. Some of you know this. You need to stand up, and you need to help us.

DR. PRABHAKARA ATREYA: Your time is up.

DR. ERIC FEINTUCH: This is America. Thank you.

DR. PRABHAKARA ATREYA: Please wrap it up.

DR. ERIC FEINTUCH: Thank you. This is the United States. We need this communication, and we need to have people have these discussions scientifically. Please review these thousand peer reviewed articles. This is our next judicial battle in Congress.

DR. PRABHAKARA ATREYA: Your time is up.

DR. ERIC FEINTUCH: Thank you.

DR. PRABHAKARA ATREYA: The next speaker is Dr. David Wilson. You have three minutes, please. Please stay in the limit of the time.

DR. DAVID WISEMAN: Hello. Can you hear me? Hello?

DR. PRABHAKARA ATREYA: Yes, we can hear you. Go ahead.

DR. DAVID WISEMAN: I'm sorry. Thank you very

much and thank you for all your work, members of the staff. I don't have no conflicts.

VRBPAC is once again asked to opine on inadequate information. Before the April meeting a *Wall Street Journal* piece posited that FDA is excluding its own experts. Next slide, number two, please.

VRBPAC were asked about the data needed to support new strain compositions. Next slide, three. What was unclear to them was that FDA just refined guidelines waived efficacy requirements. Next, slide four. FDA, everyone agrees that there is no immune correlated protection. FDA ignores its experts, notably Dr. Levy on the panel who has called for federal efforts to validate and standardize the correlate of protection. Recent vaccine decisions were based on irrelevant Wuhan immunobridging. Omicron assays are unvalidated and unverified by FDA.

Novavax may have gotten closer with there H2 assay. Any clinical relevance is refuted by CDC's analysis showing significant VE for two dose finds in toddlers with failed immunobridging but the reverse for infants. The recent stunningly noncredible efficacy

data were described by FDA as imprecise and potentially unstable. ACIP members struggled to message sprawling confidence intervals and negative waning estimates.

FDA solved this by dispensing with the efficacy data entirely, abandoning its previously used and published risk-benefit methodology. No estimate of efficacy precludes the risk-benefit analysis required for an EUA. Is this what the EUA guidelines meant when lowering the effectiveness standard to "may be effective"?

Safety questions remain. We've shown correlations between vaccination and all-cause mortality. FDA says VAERS is under and misreported. A FOIA disclosure reveals that CDC has not per its SOP conducted safety signal analyses, which we have provided to FDA. Neurological ADAs are finally being acknowledged. Still no cancer studies. CDC recommends vaccination in pregnancy despite labelling that that data are insufficient to inform risks. Next slide, five.

The central issue finally emerged when Dr. Portnoy on this Committee asked recently which cells

produce spike? How much do they produce and for how long? Pfizer dismissed this question as academic. It is certainly not.

From FOIA documents these vital studies were not done. Moderna told ACIP that the spike persists for less than a week. A Stanford study in the cell showed vaccine message and antigen persisting for at least eight weeks. The spike accumulate. Is this why myocarditis rates after boosting match your best primary series rates for some ages despite persistent contributes immune suppression, imprinting and negative efficacy? What is the toxicity of multiple doses? How will sameness of the maximum manufacturing process be defined? Are the guidelines talking about monovalence or bivalence?

Many of these concerns are reduced with Novavax. Dr. Hawkins as the alternate consumer representative today --

DR. PRABHAKARA ATREYA: Your time is up. Please wrap it up.

DR. DAVID WISEMAN: Why has FDA not consulted his gene therapy experts? Unless FDA provides this

information, Americans will have every reason to reject these "may be effective" gene therapies. Thank you and thank you to the members and staff of the Committee.

DR. PRABHAKAR ATREYA: Okay. The next speaker is Mr. Benjamin Newton.

MR. BEN NEWTON: Thank you so much for your time. You know, the question that's always before this Committee is how we can safe the most lives. You have to make these difficult decisions with limited data and do the best you can. I appreciate how difficult it is. I encourage you to let manufacturers update their vaccines, let people get boosted, and let people use the Novavax vaccine. Next slide.

A quick refresher, I presented this at the September 2021 VRBPAC meeting, and in case you've forgotten I just wanted to represented them. Next slide. Vaccine efficacy is predicted by neutralizing titers. Next slide -- so we're on slide four. Neutralizing titers decrease over time and with variants, boosters and variant matching is required. Next slide.

A year ago we had evidence that significant

Omicron-like strain drift was possible with an eightfold reduction in neutralization. Next slide, slide six. A year ago we had evidence that all people needed regular boosting to avoid mortality and morbidity associated with waning immunity and strain drift. Next slide. So how can protect be increased? We can increase the dose or frequency. Both of these increase risk from side effects, and we can do better strain matching. Strain matching is effectively a free lunch for consumers, though it does have costs for manufacturers and regulators. Next slide, slide eight.

So what are the right questions to ask? What was the cost of delayed approval of variant adaptive vaccines? How quickly can vaccines be updated, and what are the benefits? Should the FDA be involved in strain selection at all? Is there a better way for the FDA to protect consumers? Next slide, slide nine.

There are many costs associated with regulatory delaying the vaccine update, which include the Delta and Omicron waves, delayed approval for pediatric vaccines due to reduced observed efficacy, reduced confidence in vaccines, millions of people

sickened and hundreds of thousands of deaths. Next slide. So the Omicron wave, what do we know and when? Well, Moderna recalled employees to work on Thanksgiving to speed up the timeline for drug approval. They could not wait until Monday. Moderna looked at South African data and the shape of the Omicron spike. Consumers could not wait over the holiday weekend is what Moderna thought. Next slide, slide 11.

As seen in the *New England Journal of Medicine*, the efficacy drops below FDA standards of 50 percent without boosting and strain update. This drop in efficacy was caused by FTA approval delays, which prevented boosting and updating of the strain. Next slide. So what was the best case for the vaccine timeline for an Omicron booster? Moderna can go needle to needle in a personalized cancer vaccine in six weeks. The six week gap for Omicron could have been filled with wild type boosters and pediatric vaccination, reducing the R naught. Omicron specific vaccination could have started January 6th, blunting Omicron. Next slide.

It's a real question if the FDA should even be involved in strain selection process. The FDA process is long, seven months from emergence of Omicron to the FDA meeting to discuss. Manufacturers already had to start making new vaccine at their own risk because they couldn't wait on the FDA timelines. Manufactures have better incentives, personalized matching strains --

DR. PRABHAKARA ATREYA: Your time is up. Please wrap it up.

MR. BEN NEWTON: Thank you -- more effective for longer and with better safety and tolerability because of the lower dose. Companies can spend millions on strain selection and manufacturing speed because it results in better, safer, and more profitable products. Next slide, last slide.

How can the FDA best protect consumers? They can monitor and publish vaccine efficacy by manufacturer, allow manufacturers to update vaccines in weeks instead of months. They can stop preventing access to vaccines and boosters. I really thank you for your time today and for your service to the Committee. I know --

DR. PRABHAKARA ATREYA: All right. So that completes the PowerPoint presentations for the OPH sessions today. The next speakers do only oral remarks, and we'll start with Ms. Sarah Barry. You have three minutes.

MS. SARAH BARRY: Hello. Can you hear me?

DR. PRABHAKARA ATREYA: Yes, we can.

MS. SARAH BARRY: Thank you. Hello to all the Vaccines and Related Biological Products Advisory Committee members. My name is Sarah Barry. I have no conflicts, and I am the director of research and media relations for the SAFE Communities Coalition. We are a pro-vaccine nonprofit, and part of my work for SAFE involves tracking the growing political influence of the antivaccine community.

You might recall the Center for Countering Digital Hate, which found that the disinformation dozen were responsible for two-thirds of vaccine misinformation on social media. One of the disinformation dozen is a founder of a national antivaccine lobbyist group who is scheduled to give a public comment later in this session. So far this

antivaccine political organization has recruited, supported, and/or endorsed hundreds of antivaccine candidates across the United States in the upcoming elections.

In years prior we mainly saw antivaxxers focus on candidates for state legislatures, but this year this antivaccine political organization is supporting candidates up and down the ballot, from local school boards all the way up to Congress. Their only goal is to elect candidates that will use misinformation to craft policies that will weaken the public health infrastructure that has kept our schools, daycares, healthcare facilities and our communities free from vaccine preventable disease for decades.

Again, there are hundreds of antivaccine candidates up for these positions, and the risk to public health if and when any of them win cannot be overstated because the antivaccine community isn't just fighting vaccines anymore. For example, antivax lobbyists in Ohio supported Senate bill 22, which became law last year. Senate bill 22 does not mention vaccines at all, so why would they support it? Because

it gave the legislature the power to override orders issued by the Ohio Department of Health, and since the antivaxxers despise the head of the Ohio Department of Health enough to protest outside her home and practically bully her into resigning, you can see how well Senate bill 22 aligned with their interests.

Again, this isn't just about vaccines anymore. This is a movement dedicated to fighting any public health measures. Today I am appealing not only to you, the members of the Committee, but also directly to the media and anybody else frankly who will listen, especially people and influencers like Philip DeFranco, Hassan Abi (phonetic), or Under the Desk News.

The organization I'm a part of cannot fight antivaxxers effectively if people don't even understand the extent of antivaxxing influence on politics or the consequences that will follow if we don't fight back. I appreciate your time and attention today, and if anybody wants to partner with SAFE to learn more, please email us at info@safecommunitiescoalition.org. Again, that is info@safecommunitiescoaliation.org. Thank you very much.

DR. PRABHAKARA ATREYA: Thank you. The next speaker is Commission President W. Kent Carper, and you have three minutes, please. Go ahead.

MR. KENT CARPER: Thank you. My name is Kent Carper. I am the president of the Kanawha County Commission, state of West Virginia. I have no financial interests, and I thank the Committee for your kind attention.

There is an urgent need for second booster shots to protect our first responders. First responders include law enforcement, fire fighters, EMT, telecommunicators, our nurses, our doctors. It is important this be done now and not later.

Vaccine hesitancy continues to be a significant hurdle even with our first responders. During the pandemic our chief medical officer, Dr. Sherri Young, created what was called the Unified Health Command. It was also operated by our county manager and the head of our emergency ambulance authority. Dr. Young in an unprecedented move ordered the evaluation and the elevation of first responders for a priority basis to be vaccinated ahead of others.

This was done and evidence base now is proof that by doing this we were able to keep our hospitals, our correctional facilities, our police departments, our fire departments open.

This activity as ordered by Dr. Young received national attention from the President of the United States, including the White House. The evidence based data is proof that our hospitals, our fire departments, and our law enforcement were served well by this decision. We believe this is a bright line that can be utilized by the rest of the country.

We believe the FDA need to do two things. The FDA needs to recognize the need to immediately allow the distribution and the vaccination of the new generation vaccine which is more effective against the Omicron variant. Number two, we believe the FDA needs to prioritize, like was done here in the state of West Virginia, first responders to be vaccinated immediately so they are protected so they can protect us.

The time period between boosters is critical. That science is clear. This must be done now and not later. We are now seeing an additional hesitancy due

to the anticipation of the new vaccine. We believe this is another reason why the FDA needs to move further on this and not wait any longer.

The lessons we've learned here in our state are clear. We implore the FDA to allow first responders to be boosted, receive their second booster now. Their period of time between boosters is well over six months, and we believe that's what's causing the breakthroughs we see. I also anticipate a second surge this fall. Time is of the essence. I thank that Committee for your kind attention. Thank you.

DR. PRABHAKAR ATREYA: Thank you. The next speaker is Dr. Kailey Soller. You have three minutes, please.

DR. KAILEY SOLLER: Hello. My name is Kailey Soller, and I am a PhD chemist and a mother of a wonderful almost two year old. And I have no conflicts. I am very happy to say, though, that I have been protected by this wonderful mRNA technology against the most deadly virus in our recent history. Thank you so much for allowing me to speak today.

I'm incredibly thankful for the decisions made

earlier this month to approve and recommend both Moderna and Pfizer vaccines for our children under five. This was the last big step I thought I was waiting for with the COVID pandemic. It felt like an unmovable goal post, but with so many things related to COVID, we have learned that the goalposts can move and we must change because the virus itself does.

I have two points I'd like to make today. Number one, we must adapt to COVID and create the most nimble manufacturing approval process seen to date for updating vaccine boosters containing relevant, variant specific components. And number two, we must ensure that all age groups are able to receive these boosters on the same timeline.

First, regarding the need to create a nimble manufacturing and approval process for boosters, we have a template from the flu that we can start from. We know that the flu mutates rapidly every year. Therefore, we as scientists have counteracted that by changing it, updating the flu vaccine yearly. We have seen that COVID behaves similarly to the flue in that it mutates quickly, and previous vaccines aren't as

effective as an updated one would be.

Therefore, I ask you to adopt a similar mindset to what we have adopted for the flu vaccine, and in fact we must act even more creatively and fluidly than what we have done in the past with flu vaccines. The FDA must support a nimble manufacturing and approval process for updated vaccines to match the most recent variants. With the mRNA technology we are able to do this much more quickly than with other vaccine technology, and we must utilize this to our advantage.

The FDA should work hand in hand with the vaccine manufacturers to provide recommendations and ensure that boosters for COVID are as up to date as possible regarding the major circulating variants at the time. This may mean providing updated variance boosters more than the typical once per year that we see with the flu.

Secondly, we must ensure that all age groups are able to receive the updated boosters on the same timeline. As COVID mutates rapidly we cannot leave the younger age groups without the most up to date

protection. We know that these vaccines are safe.

As a scientist, consider this point. We are not changing the fundamental vaccine technology, delivery mechanisms, or ingredients beyond the specific mRNA sequence. We're simply updating the specific amino acid from the antigen presented to ourselves.

The best choice for the options under consideration today will depend on the manufacturer's ability to provide the updated vaccines to the public, but I would push for options four or five to be strongly considered. There is also a seventh option where we update the currently available BA1 bivalent booster and then push to make the BA4/5 bivalent booster available as soon as possible.

The bottom line is twofold. COVID is unprecedented. We must take an unprecedented approach and create the most nimble manufacturing and approval process seen to date to address COVID's rapidly mutating nature. And number two, these updated variance booster should be made available to all age groups at the same time. We know that COVID is here to stay. Let's ensure that we move nimbly, efficiently,

and intelligently against this virus. Thank you so much.

DR. PRABHAKARA ATREYA: Thank you. The next speaker is Dr. Ashley Serrano. You have three minutes.

DR. ASHLEY SERRANO: Thank you for allowing me to speak today. I have no conflicts. My name is Ashley, and I am here today as a mother of a three and a half year old and a clinical psychologist to many toddlers, children, teens, a few adults, but also their families. I am here today to support updating our COVID vaccines with the Omicron specific component.

March 2020 halted our lives as adults and changed the dreams we had for our children. My daughter spent her second birthday with just me and her. Her third birthday was held in a garage because it was way too cold to be outside safely, but no vaccine was available for her. So it was unsafe inside. She was able to celebrate with our neighbors in the safest way possible.

This year she wants a birthday inside. She got her first COVID-19 vaccine last week, and she was so happy. She was showing off her poke mark for days

following the vaccine. She was excitedly yelling across the street, I got my vaccine. I got my vaccine as she points to her booboo.

Mind you, she didn't experience any side effects from the Moderna vaccine last week, and she continued and continues to be her happy, energetic self. She is so excited to soon be able to go stand next to people I don't know and go into people's houses and show people my toys inside, all the things we did at three and which are all normal. I want her and all the kids to resume life as we know it or at least as much as possible.

With the currently circulating strains as well as potential for further evolution, we need to create boosters for all ages and make them readily available to everyone with ease to allow for the most protection when we need it the most, not after and definitely not two and a half years later. Each day without boosters is a day of potential illness. My daughter missed preschool yesterday and today because of COVID exposure, and we literally just got home from getting a PCR test to ensure safety for us and everyone we

encounter at work and at school.

Rather than examining the death and hospitalization rate, we need to look at short and long term consequences. As mentioned in a previous VRBPAC meeting, we do not have a full, clear picture of the harms that COVID has on developing brains and bodies, but we do know that long COVID exists and it's not a rare phenomenon. Mis-C has hospitalized thousands of children, and it is now being recognized that these severe hepatitis cases in children are likely linked to those previous COVID infections. We know COVID can cause inflammation in many organ systems, so this is not in any way surprising.

As boosters are not authorized, my daughter along with all the children who received their first shots last week will be facing the fall surge with waning protection in October, just in time for all the family and friend holidays. The rise of BA4 and BA5 is happening quickly around the world, and it's soon to be dominant here in the United States. Earlier this month it was at around 24 percent.

The risk of reinfection with BA5 has

substantially increased because prior infections are far away from aligned immune response. I don't want my daughter to continue missing out on meaningful opportunities. We need updated COVID vaccines with an Omicron specific component for all ages as children's lives are not less valuable than mine or yours. Thank you for hearing me today.

MS. JESSICA NEHRING: Good afternoon.

DR. PRABHAKARA ATREYA: Okay. Thank you. The next speaker is Jessica Nehring. Go ahead. You have three minutes, please.

MS. JESSICA NEHRING: Okay. Good afternoon. My name is Jessica Nehring, and I have no financial conflicts. Before I begin I just wanted to take a moment to thank all the members of the VRBPAC Committee for authorizing both Pfizer and Moderna's vaccines for children under five. My three year old son received his first dose last Saturday, and the joy and relief I felt once he had his first shot has been unmatched in the last two plus years.

I am speaking today in favor of updating existing boosters and vaccines with an Omicron specific

strain. I want to be able to go back to indoor concerts, sporting events, school events, my church, and family gatherings without feeling scared about contracting long COVID. I pray that these bivalent vaccines and boosters alleviate much of that inner monologue. I don't want to raise my kids constantly stuffing down my anxiety about exposure and only protection from severe illness and death.

We are learning more every day about long COVID, and the news seems to be more frightening with time about the implications of having repeat COVID infections, vaccinated or not. My hope is these bivalent vaccines will curb much of the long COVID symptoms too. We are just hoping for a better quality of life for our families but also for the masses. Unfortunately, it feels we are much behind the virus with the current vaccines that contain the Wuhan strain.

While I am grateful that our current COVID vaccines are now available to all age groups and prevent severe illness and death, they don't prevent symptomatic infection, and we are uncertain the level

of protection these vaccines give against the possibility of long COVID. Omicron is very different from the original Wuhan strain and is currently the only lineage of COVID circulating. One of the first details we were told about mRNA is how adaptable it is, so I would propose that we take these vaccines and boosters at least once a year like the flu vaccine since the dosing, safety, and efficacy have been established in both Moderna and Pfizer's vaccines.

It does not seem that we need to require pediatric trials each time a variant changes because we know the dosage sizes. Since Pfizer has announced recently that data for both an Omicron specific monovalent vaccine and a bivalent vaccine with an Omicron specific strain provided satisfactory results and Moderna has a bivalent vaccine that could be ready for mass production by late fall/early 2023, I hope that you will strongly consider authorizing these more effective vaccines and boosters as soon as safely possible so children and adults are more protected entering the school year and also cold and flu season. I really hope this is our chance as a country to get a

grip on community spread and hopefully start moving into more of an endemic phase. Thank you for giving me this opportunity to voice my thoughts and concerns.

DR. PRABHAKARA ATREYA: Okay. The next speaker, please -- the next speaker is Dr. Catharine Diehl. You have three minutes.

DR. CATHARINE DIEHL: Good afternoon. I'm a mother of two year old twins, a PhD in philosophy with a focus in medical ethics. I have no financial conflicts. I'm here today to support updating our COVID vaccines with an Omicron specific component.

I recommend updating our boosters with a composition closer to currently circulating variants but also streamlining the regulatory process. The fast mutating character of the SARS-coV-2 virus means that we must harness this benefit of the mRNA platform to change strain composition in response to variants of concern. We should take our responses to the flu as a model and accelerate them further.

Recent studies show that BA4 and 5 variants exhibit significant immune escape. Broad neutralization against BA4 and 5 does not occur in

individuals vaccinated and boosted with the current formulation of vaccines, even after BA1 breakthrough infection. This raises substantial concern.

First, in addition to immediate pain and discomfort, illness results in time away from work and school, leading to negative economic and social consequences. Second, preventing infection is currently the best way to prevent long term consequences of COVID-19 disease. These include but are not limited to increased risk of type 1 diabetes, autoimmune diseases, hepatitis, cardiological and neurological impairment, post COVID-syndrome, as well as increased morbidity and mortality from a variety of causes.

Additionally, the substantial immune escape exhibited by BA4 and 5 also suggests there might be further decreases in protection against severe disease. Both sponsors' updated boosters demonstrate substantial increases in neutralizing titers against BA 4 and 5 with significant gains in efficacy expected. Additional gains would likely be provided by a BA4/5 specific formulation, but these gains must be weighed

against the delays in the production process that would be caused by switching strand composition. In particular, I urge the Committee to streamline recommendations for all age groups six months and up.

At this stage there is little reason to require separate pediatric trials for updated boosters and doing so would only leave our children unprepared to confront the following winter wave. More broadly, however, we must harness the power of the mRNA platform to quickly pivot to do variants of concern. Including an Omicron specific component is the first step, but it will not be the last.

We cannot continue to be six months behind emergent variants. Our response must be far more nimble. I respectfully request that the Committee issue guidance to allow for such an updated response.

Finally, I wish to speak briefly regarding some remarks one of the voting members of the Committee at the last VRBPAC. This Committee member chose to criticize parents who spoke in favor of vaccination, implying that our risk calculations were inappropriate and uninformed. This member offered a false comparison

between the risks of COVID-19 and the odds of a child being struck by lightning.

The comparison is incorrect. Kids under five are by an order of magnitude more likely to die of COVID-19 than to be struck by lightning. More significantly, death is not the only bad outcome and not the only one informing parental decision.

Now these remarks have been made into a meme and shared by antivaxxers in order to harass pro-vax parents. The member's comments have fueled misinformation, and it's inappropriate to include on this Committee someone who would pander to the irrational destructive forces in our society. Thank you very much.

DR. PRABHAKARA ATREYA: Thank you. The next speaker is Kate Schenk. You have three minutes.

MS. KATE SCHENK: Good afternoon. Thank you for allowing me the opportunity to speak today. My name is Kate Schenk. I have no conflicts.

I'm speaking today to advocate for the inclusion of an Omicron component in COVID-19 boosters for everyone, including children. I'm the mother of

three children under the age of five. Last week all of my children received their first Moderna vaccine, and I am so grateful that they are finally on the road to protection from COVID.

My two and four year old daughters have been saying that shot wasn't so bad and we were so brave. Other than one mild sore arm none of my children experienced any side effects from the vaccine. They're all playing and acting as usual, and my seven month old son even started pulling up on furniture the day he received his vaccine and is crawling faster than ever. Clearly receiving the vaccine has not slowed him down at all.

One of the most significant reasons the under-five vaccine was so important to my family is because my oldest daughter will be starting kindergarten in September. After two years of mainly staying home and seeing very few people, she will truly be venturing out into the world for the first time. The start of school is a bittersweet moment for many parents, but I think it's particularly difficult for those of us who have done everything possible to protect our children from

COVID while awaiting the vaccine.

The fact that my daughter will be fully vaccinated before school starts eases some of my concerns, but we know the primary series does not protect against infection from COVID strains that are currently circulated as much as we would like. Unfortunately, COVID has mutated rapidly since the beginning of the pandemic. The current COVID vaccine demonstrates continued protection against severe illness and death, but those are not the only outcomes that should concern us.

Omicron has proven to escape immunity and is highly transmissible, and even mild infection equals time lost from the workforce and absence from school. Additionally, we are still learning about the impact long COVID has on individuals as well as society as a whole. We know COVID can effect multiple organ systems with devastating consequences. Preventing infection from these new strains will reduce the likelihood of developing long COVID.

An updated booster containing an Omicron component will give us the best chance of avoiding

infection this fall. This is an opportunity to utilize the power of mRNA technology to adapt to the current threat. I would especially like to reinforce the importance of including boosters for children when making a decision regarding updating COVID boosters.

The wait for the primary series of boosters -- the wait for the primary series of COVID vaccines for our children, especially those under five, was long and excruciating. We cannot let this happen again. Children need to be eligible to receive these updated boosters alongside older cohorts, not lagging behind unprotected. Failing to include children will leave them vulnerable this fall, which will negatively affect families.

As a parent sending a child to school it would reassure me to know that my children will receive the most up to date protection available, giving them the best hope at avoiding infection from the currently circulating COVID strains. Please allow everyone equal protection going forward. Thank you for your time today.

DR. PRABHAKARA ATREYA: The next speaker is

Aime Baker. You have three minutes.

MS. AIME BAKER: Thank you for hearing my statement and I have no conflicts. I understand that the context of today's meeting is for the Committee to discuss and advise on the modification of the strain composition of future COVID-19 vaccines. I also understand that there's very little I can say today that will make a meaningful change in the outcome of your recommendation.

You have reviewed the available data, safety profiles, and epidemiological context that is relevant to this discussion, and I trust that you will vote in the best interest of science, safety, and public health welfare. So what I want to tell you about today is something that you might not know. I'm a mother of two children, ages one and three. They each received their first dose of Moderna's under five COVID vaccine last week, and we could not be happier to finally after so much waiting have had this opportunity.

Our journey to obtain this vaccine however was not without challenge. Information about its availability has not been delivered to healthcare

providers in a satisfactory way. State and local health departments across the country have been entirely inconsistent in their approach. Parents of children who want to find vaccines have had to crowdsource through information through social media because in many cases they cannot receive reliable information from any official source. The lack of urgency in this manner which has been perpetuated by some members of this Committee who would seek to minimize the importance of pediatric vaccination is hard to comprehend.

I understand that this is not a problem that is necessarily in this Committee's purview or the topic of today's meeting. Nonetheless, this is a problem, and a regular person like me has no means or authority to invoke change. I have spoken to my pediatrician who instructs me to speak to the medical group, who instructs me to speak to the pediatrician. I've spoke to the frontline staff of my health department whose responses have varied from the vaccines are not yet approved to we have no intention of ordering any vaccines. Both statements are materially false, but I

only know that because I've worked tirelessly to try and find answers.

And all this is coming from a part of the country where vaccine uptake is relatively high. I can only imagine how difficult this has been in other parts of our nation. I'm telling you these things today because I hope that some of you listening may have the authority, connections, or purview necessary to instill actionable change going forward.

We face a crisis of health misinformation and antivax sentiment in our society, and your messaging matters. When you consider new formulations for booster shots, please consider how you can deliver well-organized, timely, and accurate information to healthcare providers. Many children will be due for the second dose of their primary series in a few short weeks. Please include all ages for immediate eligibility for bivalent vaccines.

This will not only have the benefit of simplifying your communication and messaging, but it will also finally afford our youngest the same amount of protection that we have benefited from all along.

If you delay changes for younger age groups, you will lower vaccine effectiveness for those groups. It will damage vaccine uptake, and you will continue to erode public trust in an antiquated process that no longer fits the needs of our modern world. Thank you for your time and also Corey's phone got hung up.

DR. PRABHAKARA ATREYA: Thank you.

MS. COREY C.: Hi, I am here now.

DR. PRABHAKARA ATREYA: (Inaudible). This is Corey C. She's going to be presenting. You have three minutes.

MS. COREY C.: Good afternoon. Thank you for the opportunity to speak to you again today. I have no conflicts. As we discuss the plans for the future of COVID vaccinations in the country, I want to briefly cover the history as it pertains to protecting our youngest citizens.

When I spoke last time, I was dismayed to hear some Committee members express shock and outrage that parents waiting for the chance to vaccinate their babies distrusted the FDA's response and perceived a lack of urgency. So let's review the facts. Parents

were told repeatedly that the vaccine was coming soon or in a matter of months. Multiple delays occurred and were explained with an ever changing list of reasons.

As Moderna approached the submission a statement was made that the VRBPAC meeting would not be delayed to wait for Pfizer, only to see Moderna wait almost seven weeks for a meeting to be scheduled without more explanation than "it's complicated." Miraculously, the VRBPAC meeting was scheduled the same day that Pfizer started their submission. Our concerns and suspicions were reasonable in view of this history. This saga represents a failure of communication and as of yet no convincing explanation has been given.

In an effort to improve the understanding of the experience of parents with kids under five, I conducted a simple survey on the recent rollout. Out of 200 parents surveyed almost all cited access to boosters, especially variant specific varieties, and preventing future delays as their top concerns. Ninety-four percent of those not enrolled in either study chose Moderna for their children, and most rated the time to protection as their top deciding factor.

Time is precious, especially for such young children. After approval, 51 percent had to spend more than three hours actively finding an appointment, and a third spent over five hours. The top reasons cited for a lack of appointments were vaccines not yet delivered, pediatricians not offering them, and difficulty in finding Moderna specifically.

When an appointment was finally found, it was overwhelmingly from discussion on social media with very rare success from government official sources. Families had to wait an average of one week from searching to first vaccination appointment, and a quarter of families had to spend more than one hour driving one way to that appointment. I realize this is not the purview of this Committee, but I wanted you to have that visibility into our experience as well as others listening on this call that may be in their purview.

Why was this such an ordeal for something we knew was coming for months? This fumbled rollout combined with the delay history paints the picture of a population that has been consistent afterthought in

this deadly pandemic, our precious babies, our future. A variety of recent events has shown that as a society we say that we care deeply for the lives of our children but appear unwilling or unable to make the decisions that actually protect them. We've been enormously lucky thus far that this pandemic has not been as devastating as it might have been for our youngest. We may not remain that lucky forever.

I'm immensely grateful for the miraculous vaccines and this Committee's work to recommend approval. However, your work is not done. I recommend this Committee to recommend approval of Omicron specific vaccines for all ages as soon as possible in addition to making them available as both primary and booster doses to remove --

DR. PRABHAKARA ATREYA: Your time is up.

MS. COREY C.: -- our confusion.

DR. PRABHAKARA ATREYA: The next speaker is Dr. Katarina Lindley. You have three minutes. Go ahead, please.

DR. KATARINA LINDLEY: Good afternoon. I'm Dr. Katarina Lindley, family physician and member of

Global COVID Summit and steering committee of the Global Council for Health. I have no conflicts of interest. mRNA technology combined with lipid nanoparticle is a key component of the recent Pfizer and Moderna vaccine mass rollout under EUAs. It should be recognized that 18 months on the mechanism of action in pharmacodynamics of this mRNA LNP platform is still only partially understood. To assume that the platform is intent to be safe and doesn't require case by case safety assessment and regulatory scrutiny is in my opinion reckless and runs counter to the very purpose of a drug regulator.

Each component in the mRNA (Inaudible) program to expect is unanimous to new chemical entering the body and should be treated as such with more regulatory scrutiny to test long term safety. We know already that LNPs and their cargoes move great distances from the site of injection into the body and blood circulation. (Inaudible) detected in the spleen, brain, heart tissue, bone marrow, adrenal (Inaudible). How can we move forward when pharmacokinetic studies have already shown there is spike production in

reasonable (Inaudible) of two months or longer?

Not only should the LNPs have been administered in healthy people, everything you are calling for must be addressed with more scrutiny. Available biodistribution and pharmacokinetic studies to date reveal a very different picture of what happens following injection compared to the oversimplistic and predictable picture presented by health authorities and vaccine manufacturers. Safety signals are now clearly evident, yet utterly ignored.

VAERS data alone which is significantly underreported shows 1.3 million COVID-19 injection harms with over 28,000 reported deaths. Many of us who have been dealing with the fall out of the speedy rollout of the new technology have much graver concerns than those reflected by the VAERS data. We are dealing with significant increase in complex neurological, endocrine, autoimmune, and cardiac issues.

You have to be a gambler or something much worse to argue there is no risk of fertility issues, which could be catastrophic for our future generations. Has the FDA really learned nothing from the

thalidomide, Vioxx and other regulatory disasters of the past? As a reminder, the FDA mission statement states "The Food and Drug Administration is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices."

The FDA needs to remember that its responsibilities are ultimately to the people of this great nation. That includes the deep responsibility to children and our future generations. My expectation is that FDA will continue its mission of protecting public safety and best interest against any and all harm. Future framework for this new technology is an existential threat to the public health and should not be approved. Thank you for your time.

DR. PRABHAKARA ATREYA: The next speaker is Valerie Borek. You have three minutes, please.

MS. VALERIE BOREK: Hello. Thank you for this opportunity to comment. My name is Valerie Borek. I am policy analyst for Stand for Health Freedom, a national grassroots organization over a half million Americans who are advocates for informed consent and no

medical mandates.

Americans have a constitutional right to informed consent. I urge you to uphold your mission to ensure safety and efficacy of COVID shots before voting on strain replacement without FDA reviewed clinical trials. Informed consent requires disclosure of risks, benefits, and alternatives in terms a patient or guardian can understand. They must be able to ask questions and get answers from providers who have the information they need to be able to answer those questions.

The FDA claims Americans aren't entitled to informed consent for EUA products, but that is not true. Health professionals have a duty to their patients including informed consent. EUA products are not fully approved by the FDA and are therefore experimental, requiring informed consent under U.S. law. One of the first U.S. Supreme Court cases addressing COVID policy the Court affirmed that, quote, we don't cut the Constitution lose in a pandemic.

Chief Justice Roberts wrote, "As more medical and scientific evidence becomes available, courts

should expect policies that more carefully account for constitutional rights." Over the last two years the FDA has lowered their standards, using antibody response instead of effectiveness when you do not have clinical data that we'd all love to have, to quote Dr. Rubin in the April VRBPAC meeting, is not legally, medically, or scientifically sound.

Regarding waning immunity and boosters, Dr. Weir admitted, quote, there's just an awful lot we don't know. Dr. Meissner asked why SARS-coV-2 mutates more than other viruses and was told the spike protein in the shots is driving the rate of evolution. In other words the shots made the mutation, yet the FDA has not investigated this.

In CDC's ACIP meeting on June 23rd, members asked about the difference between the Pfizer and Moderna formulations for our babies and toddlers, but no one could answer. This is not informed consent. The FDA has not explored known potential risks, which is required for an EUA, and therefore cannot legally authorize any shots.

The FDA is ignoring massive safety signals

from VAERS and reports of injuries or death from shots made in Advisory Committee meetings, in Congressional hearings and in the federal register. The shots were rushed a warp speed with expedited FDA review, and clinical trials are ongoing through 2024. There's no long term safety data for this novel mRNA technology.

The FDA has not addressed fraud allegations made by Dr. Peter Doshi or Pfizer employee Brooke Jackson, nor has it answered U.S. lawmaker concerns about authorization of shots for babies and toddlers. Studies were unblinded, confusing data and eliminating controls. VRBPAC and ACIP members continually say they need more information about natural immunity and safety. How can the FDA tell parents or doctors that benefits outweigh the risks when you do not know the risks?

Even less is known about strain replacements for COVID shots. Americans need this missing data to make informed medical decisions. The more trustworthy your data the more confidence Americans can have in your advice. It is illegal for the FDA to authorize COVID shots without adequate safety or efficacy data.

The FDA's policy of shots first, questions later does not allow for informed consent. On behalf of the Stand for Health Freedom, I thank you for your time.

DR. PRABHAKARA ATREYA: Please wrap it up. Your time is up. Thank you. The next speaker and the last speaker is Dr. Hershie Klein. You have three minutes to complete. Thank you.

DR. HERSHIE KLEIN: Thank you for letting me speak today. I'm Dr. Hershie Klein. I have no conflicts (Inaudible) already proved that there is no emergency. The pandemic is long gone so your (Inaudible) forced vaccinations has no validity.

Pfizer and Moderna have been shown to have falsified their placebo controlled trials. Allowing Pfizer and Moderna to do their own studies is like the foxes guarding the hen house. There's a principle (inaudible). If you lie on one thing, then you are a liar, period, and you are not to be believed about anything. When the ban on Prilosec expired Astro-Zeneca made a slight change in the molecular structure of Prilosec and came out with Nexium, which has a much worse side effects profile than the similar drug,

Prilosec.

Allowing Pfizer and Moderna to change the molecular structure of the original Wuhan vaccine and claiming similarity to it is trying to sneak in drugs or bioweapons that have not had any placebo controlled double blind trials for at least five years, including long term complications and adverse reactions. How can you have moral and intellectual integrity and allow this sleight of hand to become law? (Inaudible)

At the meeting of 4/6/22 Dr. Jerry Weir said, "We can predict the behavior of influenza virus, by the SARS-coV-2 is not predictable." He also says one of the conditions for changing COVID-19 strains composition is vaccine manufactures must have clinical data to support the safety and effectiveness of modified vaccines for their respective products. And now you're about to throw caution and safety out the window in complete contradiction to what Dr. Weir clearly said.

How do you sleep at night? Since the evidence in previous studies has previously been either completely ignored or fraudulent or manipulated, it

seems that you are willing to give preapproval for changes made without any studies at all. It seems like you are contemplating disbanding the FDA because essentially you are advocating no safety testing, that these vaccine manufacturers can just change the mRNA and no additional study needs to be done and no clinical trials.

The next logical step in that process would be to disband the FDA because what's the point? I'm sure big pharma would love to have you work for them at a really good salary. Dr. Ryan Cole a world renowned pathologist, immunologist, and virologist said this is not a traditional vaccine. A traditional vaccine doesn't replicate. The current vaccine's replicated by injecting a gene into someone's body in a lipid nanoparticles, which goes to every cell and makes your body a spike protein factor, and that spike is a toxic (Inaudible) spike.

Omicron has already mutated 38 times. By the time you come up with a modified vaccine, even if you do away with safety testing which is totally unethical and unscientific, Omicron would have mutated multiple

times, and your vaccine will be ineffective and will cause more severe adverse reactions as Nexium did and (Inaudible) deaths. You are holding the future of humanity in your hands.

If you vote to not allow the vaccine manufacturers to be able to change their vaccines without long term clinical trials for safety and efficacy whenever they want to going forward, then you will have taken the first step to saving humanity. If you vote to allow them to have the freedom to make changes in the vaccines at will going forward, then there will be no humanity to save. Humanity will cease to be, god forbid. May the almighty give you the courage to say no to this proposal and choose life.

DR. PRABHAKARA ATREYA: Dr. Klein, your time is up. Can you wrap it up?

DR. HERSHIE KLEIN: Thank you.

DR. PRABHAKARA ATREYA: Thank you. And that concludes our open public hearing session for today, and now I hand over the meeting back to Dr. Monto, our chair. Dr. Monto, take it away.

DR. ARNOLD MONTO: Thank you so much, Prabha.

We now have a ten minute break, so we reconvene at 2:45 Eastern Time. Ten minute break.

MR. MICHAEL KAWCZYNSKI: All right. Let me set the timer here. All right. 15 minutes. And all right. Studio, if you wouldn't mind --

[BREAK]

COMMITTEE DISCUSSION OF QUESTIONS

MR. MICHAEL KAWCZYNSKI: All right. And welcome back from that short break. We are going to get reconvened here. You probably saw a little bit a slide shuffling, and I'll let our Chair Dr. Monto, express what's happening. Dr. Monto, take it away.

DR. ARNOLD MONTO: Thanks, Mike. We're going to have a brief catchup session in which we will finalize or get answers to some of the questions that actually arose during the morning. We're going to hear from Dr. Marks, Dr. Scobie, and then a Pfizer representative before we go back to Dr. Weir with the discussion questions. So Dr. Marks.

DR. PETER MARKS: Thanks very much, Dr. Monto. So I first of all want to thank everyone for listening through the open public hearing. Again, I just want to make sure that we understand that FDA does not necessarily concur with anything that was said at that hearing, and once again, I would reiterate that the VAERS system is an adverse event reporting system, which is a joint responsibility of the Centers for Disease Control and Prevention and the Food and Drug Administration.

We take safety monitoring very seriously, and what is on the external facing portion of VAERS is not necessarily -- does not necessarily mean those events were associated with the vaccine. We actually do a quite thorough analyses, and as is clear from analyses not just through the United States but through multiple European and Asian health authorities the vaccines that we have deployed here in the United States are actually have very favorable safety profiles.

So that being said I wanted to just show the Committee that while we were meeting earlier this morning, the CDC has updated its Nowcast website with

the most recent nix of variants isolated during the past week, in other words through June 25th for which data are available now. And you can see that we now have BA4 and BA5 combined make up just over 50 percent of the variants that are being seen, so as predicted BA4 and BA5 are squeezing out the other Omicron variants at this point.

So I want to just leave you with that, and I want to turn it over back to Dr. Monto. I think there were a couple of other questions that will be answered now.

DR. ARNOLD MONTO: Thank you. Now, Dr. Scobie, there were some questions raised, and you had some PowerPoints to answer them.

DR. HEATHER SCOBIE: Yes, can you hear me?

DR. ARNOLD MONTO: We can.

DR. HEATHER SCOBIE: Great. So the first question was whether there were any changes in Mis-C reporting during Omicron, and I have pulled this data off of the COVID data tracker. And you can see towards the right side of the graph that during the Omicron wave we still continued to receive reports of Mis-C

during Omicron, but the number was probably not as high relative to the number of cases that were reported as they were in previous waves. And that's probably multifactorial, including pre-existing immunity from COVID vaccination or prior SARS-coV-2 infection, as well as differences in clinical disease associated with the Omicron variant compared to previously circulating variants.

And I believe it was mentioned that a recent Danish study found that the risk of Mis-C after SARS-coV-2 infection during the Omicron wave was substantially lower than previous SARS-coV-2 variants, and they also found that the risk of Mis-C during Omicron was significantly lower after breakthrough infection in vaccinated compared with unvaccinated children and adolescence. So that's another important take-home.

The next question I was asked was about trends in cases and death by race and ethnicity, so this date is also off of the COVID data tracker. It shows the percent of the U.S. population that those various groups make up in grey and then the percent of cases in

light blue and the percentage of deaths in dark blue attributed to the different groups. And you can see that white persons make up less of the cases overall but a larger percentage of deaths, and the opposite is true for Hispanic and Latino persons.

They make up a larger proportion of cases, but their percentage of deaths is slightly lower than their composition in the population. And for multiple and other non-Hispanic, that group, they have a larger percentage of cases than their composition in the population, and their deaths are about even with their distribution in the population. And when you look over time the trends are essentially similar, so I pulled these data off too.

You can see for deaths by race and ethnicity in recent weeks that rates in white persons are higher than other groups. Another question I got was about -- or Ruth got which I'm responding to was the percentage of cases being sequenced and any bias in who is being sequenced. So this varies by week, but about 5 to 10 percent of PCR confirmed cases are sequenced weekly in recent weeks. This did get down to one percent during

the peak of Omicron reporting, and that was because of the overwhelming number of samples that were processed during that time.

We know this breakdown by state, and we have about 2 percent to 20 percent of all PCR specimen sequenced by state. So we indeed do have certain states that sequence a lower proportion of cases, but we do attempt to adjust for this in the weighting approach that we use. We also have some indication that hospitalized cases may be underestimated in this group because of our current sampling framework for genomic surveillance, so a lot of the sequenced cases at least to date have been coming from basically outpatient settings or testing clinics. I hope that answers the questions, but I'm willing to clarify.

DR. ARNOLD MONTO: Thank you, Dr. Scobie. It sure does. Now, I believe Pfizer had some supplementary information as well.

DR. KENA SWANSON: Yes, thank you. Hope you can hear me as well.

DR. ARNOLD MONTO: Yes, we can.

DR. KENA SWANSON: Great. So we wanted to

follow up from this morning's question from Dr. Doran Fink who asked how the BA4/BA5 neutralizing responses compared between a booster with an Omicron BA1 containing vaccine versus a BA4/5 modified vaccine. And so as shown on this slide what you are seeing here is the monovalent Omicron BA1 vaccine given as a booster, and that's shown in the bars in blue on the left. And in the middle and the right as shown before are the BA4/5 monovalent groups in red and the BA4/5 bivalent in purple.

And as you can see the BA4/5 neutralizing titers were 11.3-fold higher in the monovalent BA4/5 vaccine group and 4.8-fold higher in the bivalent BA4/5 vaccine group compared to the Omicron BA1 as a booster. So what you can see is the responses against also the reference strain and other Omicron sublineages such as BA2 and BA2.12.1 were similar or higher compared to the BA1 vaccine group. So I just wanted to share that data to follow up and happy to take any questions either now or during the open session.

DR. ARNOLD MONTO: Does anybody have questions of this Pfizer data? I think that's critical before we

move further because -- okay. Let's park any questions until later on. Now we go to Dr. Weir who is going to bring up the discussion topics, and we'll go straight into the discussion. And if questions come up, we'll take them as we go through the discussion. Dr. Weir.

DR. JERRY WEIR: Thank you. I don't see the questions on the screen, though.

DR. ARNOLD MONTO: Not yet. It says -- there we are.

DR. JERRY WEIR: Ah, there they are. There they are. Do you want me to read them, Dr. Monto?

DR. ARNOLD MONTO: Yeah. Why don't you read them and comment on them? And then I'll make my comments about various weight.

DR. JERRY WEIR: Okay. I think Dr. Marks read them at the start of the meeting, but I'll read them again. We have several discussion questions, and I think the number of the discussion questions reflects the complexity of what we're dealing with here today. The first one is "Please discuss the various considerations involved in updating the strain composition for COVID-19 vaccines in the U.S. Please

provide input on the following and discuss whether additional data are needed to facilitate a recommendation."

First of all, "Is a change to the current COVID-19 vaccine strain composition necessary at this time?" I'll just read them all first, and then we'll go back. The second one is "Please discuss the evidence for the following," and we have 1, 2, 3. One is the selection of a specific Omicron sub-lineage. In other words as you've already heard there is a question of whether we go with something such as BA1 that we have data for or BA4/5 which we have somewhat less data for.

Please discuss the evidence supporting a monovalent or a bivalent containing a prototype plus Omicron, and please discuss the evidence supporting or extrapolating the available clinical data for modified vaccines to different age groups. The second one is what additional data, if any, would be needed to recommend an updated composition of the primary series vaccine? If the booster vaccine composition changes -- in other words if the Committee recommends it and we

recommend it -- would continuing to use the prototype primary series vaccine this fall still be acceptable? So those are the discussion questions. Any questions about the questions?

DR. ARNOLD MONTO: Well, and I noticed that we basically have a little over an hour to go through all these questions. What I think we are going to have to do is talk about the items that are most specific and let the issue of what additional data would be necessary to flow from that rather than go through these questions related to specific data separately. So --

DR. JERRY WEIR: Okay. The first one is actually pretty specific, even though it's a discussion question. Is a change to the current COVID-19 vaccine strain composition necessary at this time?

DR. ARNOLD MONTO: Okay. Let's start the discussion on that one, so we've got lots of hands raised. Dr. Offit.

DR. PAUL OFFIT: Thank you. So first of all I feel comforted by the fact that we're jumping with a net. I mean, to date the current prototypical

vaccines, the ancestral strain vaccines do protect against serious illness. We don't yet have a variant that is resistant to protection against serious illness.

We were asked in this meeting to see whether or not -- well, it's clear that this 1.75-fold increase of neutralizing antibodies induced by the Omicron bivalent strain above the ancestral strain is clearly statistically significant, but the question is it clinically significant. And that's what's not clear. I mean, we don't have a clear efficacy correlate to what 1.75 means.

In fact the WHO physician that presented, Dr. Subbarao, showed a slide actually from Bob Cedar's group, which is, you know, the NIH group. I think Matthew Gadney (phonetic) was the first author, but what that study was in nonhuman primates was they gave three doses of the ancestral strain with two doses of the ancestral strain with an Omicron mRNA booster and then (Inaudible) with Omicron. And there was no difference, so not terribly comforting.

And then as we note know we're up to 50

percent of the circulating strains are B4/B5, so that 1.75 figure is really meaningless. You know, we know that the neutralizing antibodies against Omicron you can probably divide by three to see what the neutralizing antibodies are from B4/B5. It was disappointing to me in the Moderna presentation that they get -- they test neutralizing antibodies against B4/B5 after the Omicron boost but don't test the ancestral boost when that's exactly what you want to know.

So finally, I'll close with this. I think what Dr. Hildreth said the last time we talked, which this is a new product, and I think as a new product it should be handled as a new product. And when the WHO says that, you know, this may be of value I just think we need a higher standard for protection than what we're being given. I think it's uncomfortably scant so thanks. Thanks for your attention.

DR. ARNOLD MONTO: Dr. Gellin, followed by Dr. Marasco.

DR. BRUCE GELLIN: Can you hear me?

DR. ARNOLD MONTO: Yep.

DR. BRUCE GELLIN: Yes. Thanks. No, Jerry, I think this is for you. It's really in the preamble, and this may be out of scope for this Advisory Committee. But it's about the composition of vaccines in the U.S. And given the manufacturers, that these are global manufacturers, do we have any implications of what the downstream impacts are going to be of changing the production and what that might mean for supply elsewhere?

DR. ARNOLD MONTO: Do we have an answer to that?

DR. JERRY WEIR: I don't have an answer for that. I mean, I think we could ask the companies themselves what affect it would have on their production globally. I don't know how it would affect other companies that are not authorized in the U.S. I really don't have an answer for that.

I mean, you're right. There are quite a few other companies that have authorization in other countries, and I don't know what it will mean, though I think Dr. Subbarao mentioned a little bit about that factored into their consideration too and why they

first of all wanted to maintain a primary series of the current vaccines. But I don't have anything else to add, Dr. Gellin.

DR. ARNOLD MONTO: Okay. Dr. Marasco, followed by Dr. Chatterjee.

DR. WAYNE MARASCO: Thank you. So I don't know if the rest of the Committee was as impressed by this data as I was, but the Novavax data was pretty significant in that the ancestral strain in their formulation was able to give, you know, pretty good protection against Omicron 5. And they also showed in their cartography work that the antigenic distance had been lessened with that booster.

So that essentially means that the antigen itself presented properly in an adjuvated protein form is able to produce antibodies that have that broader capability, and I'm wondering after seeing this data if we're not witnessing some of the limitation that there may be by the mRNA vaccines. Yes, they were first out of the gate, but they don't appear to be able to have that kind of breadth of protection. So really the question is do we need to change the COVID vaccine

strain composition. I think the answer would be depending on what the vaccine is, at least in my eyes from the data that I saw. Thank you.

DR. ARNOLD MONTO: Dr. Weir, we are mainly -- we're talking across the board about all vaccines, but in reality it's the mRNA vaccines that are most in question right now. Is that correct?

DR. JERRY WEIR: That's true because that's the data that we have. I would just caution you that one, the data presented by Novavax hasn't been reviewed by the Agency. That's one thing.

The other is it's very difficult to make comparisons between studies done by different companies like this and try to draw broad conclusions. It's hard enough what we're doing looking at the mRNA data to ask whether the inclusion of an Omicron component is beneficial and improves the vaccine. That's the only candidate vaccine data that we have.

I think it is encouraging that two different companies, both mRNA vaccines, gave somewhat similar results. But it does become more and more difficult then to compare to other studies like the one you

mentioned.

DR. ARNOLD MONTO: And isn't it also the case that we really are talking about a new event, the boosters that would be given in starting October?

DR. JERRY WEIR: Say that again, Arnold. What do you mean?

DR. ARNOLD MONTO: We're talking about a new episode in our long lines of boosters, et cetera, that this is something which would be given in October.

DR. JERRY WEIR: That is based on the timelines that we know about -- that's probably what would be realistic, yes.

DR. ARNOLD MONTO: And not before. So we're trying to predict the future.

DR. JERRY WEIR: Well, again -- yes, we're trying to predict the future. Trying to be prepared for the future I guess is a better way then predicting it.

DR. ARNOLD MONTO: A better way to put it.

DR. JERRY WEIR: Okay.

DR. ARNOLD MONTO: Okay. Dr. Meissner, followed by Dr. Hildreth.

DR. CODY MEISSNER: Thank you, Dr. Monto. And first I'd like to thank Dr. Weir for helping us put this question in perspective, and it's an extremely complex issue. I think my thoughts are that we don't know how this virus is going to mutate, whether it will be a variant of BA5, BA4, BA1, or will it be a completely new lineage.

I think that what Dr. Offit said is that -- I think quite accurate, that so far we haven't seen variants that cause more severe disease. What we're seeing is increasing transmissibility, increasing R naught, or that is replication of this virus. But so far it's probably going to be like the seasonal coronaviruses which evolve and escape resistance from our antibody or our immune response from the year before and then recur but don't cause more severe disease. And so I think obviously we can't predict if this is going to happen.

The real question is will the strain mutate so it's resistant to the immunity that's generated by the vaccines? And it's very hard to tell when that will happen. I think it's likely that we will need an

update to what's -- to the strain that's present in the mRNA vaccines, but I don't know when. My sense at this moment is that we're not there yet, but I don't know.

And the other question that isn't part of the discussion that worries me just a little is that we haven't discussed safety. And if we have a bivalent vaccine that makes antibody to two types of or two variant spike proteins, what is that going to do to the risk of issues such as myocarditis? We need more study, more research into what is the association with vaccines and the mRNA vaccines and myocarditis, but one reasonable theory seems to be molecular mimicry and cross-reactivity with some of the alpha-myosin molecules in the muscle. And might we increase the risk of that if we use a bivalent vaccine? I don't think we can answer that, but I do think it's a safety issue that should be considered. Thank you.

DR. ARNOLD MONTO: Thank you, Dr. Meissner. I just want to remind the Committee of the discussion that Dr. Subbarao concluded with, and that is that in strain selection typically in the past for flu but now for SARS-coV-2, what they are looking at is increasing

the breadth of immunity. And it was in that regard that she answered that an Omicron booster would be the one which would increase the breadth of immunity, not knowing what the next variant is going to be.

So that is something which we need to consider because one thing that is clear is that there is waning of immunity and boosters are going to be necessary. So we're talking now about a booster that will inevitably be necessary. We've heard in the open public hearing that some people wanted to increase the number of people available for fourth doses. That's the issue of the necessity for boosters. Dr. Weir.

DR. JERRY WEIR: Yeah. I just want to echo exactly what you're saying, Dr. Monto. I mean, the overwhelming odds are that whatever is around in the fall will still be closer to whatever Omicron component is there than it will be to the original prototype Wuhan Washington strain, and I think that's what Dr. Subbarao was trying to get across about broadening the response, to not trying to predict the exact strain but trying to get something that will still give an improvement because it's much closer. I would agree

with you completely.

DR. ARNOLD MONTO: Okay. Dr. Hildreth, followed by Dr. Gans. It looks like we're going to spend the whole afternoon answering the first discussion question.

DR. JAMES HILDRETH: Thank you, Dr. Monto, and thank you, Dr. Weir, for the information you provided us. I just have three thoughts to share. One is I mentioned this last time that these new vaccine derivatives are sequences -- are new substances, and I just wonder whether or not they need to be more carefully tested for safety. Maybe some electro mimicry could cause antibodies. I mean, there are a lot of things that are possible. I just think that we have to be more careful about using these new vaccines without more thorough testing.

The most compelling thing that I've seen today is the data from Novavax showing that their protein vaccine can illicit neutralizing antibodies to the prototype strain, to BA1, BA2 and BA5. I mean, their data seems more impressive to me than the data presented by Pfizer and Moderna, so I just wonder

whether or not it might be timely for the Agency to quickly review the data and make a decision to approve the Novavax vaccine because it'd be much more simple to have a single vaccine to use for both the primary series and the boost to cover the variants.

And there are tens of millions of people who've not been vaccinated, many of whom would accept a protein vaccine who would not otherwise accept an mRNA vaccine. So to me I think it's very compelling that we move forward on the Novavax vaccine for all those reasons. And, again, I want to say that the most impressive data that I saw today was presented by Dr. Glenn from Novavax, and I'll just stop at that.

DR. ARNOLD MONTO: Dr. Gans.

DR. HAYLEY ALTMAN-GANS: Thank you. I just wanted to add to the discussion as to other points of view. I would agree that the data presented from our colleagues at Novavax was very impressive, but I don't think that that's something we would bring forward in a vacuum, that there's plenty of people who have had the current messenger RNAs. And there's clear evidence that there's a way to actually improve upon our

response and broaden that immunity as has been brought up, and I think that's really important for several reasons, not only so that potentially it would actually expand into variants that we actually haven't seen.

But it's actually shown to be more persistent, and so broadening our T cells as well as our B cells. And there is T cell data that these companies aren't generating but that other of our colleagues are publishing, and so I think that that would proport to a longer lasting, which is really important in terms of how we look at these vaccines coming forward because we obviously don't want to be boosting as frequently as we have since that's going to be important.

So I think that we have to consider that the current composition should be changed and there is data that is also out in print that is -- the variants that we choose is along the lines of the B4/B5, that that actually would cover other of the Omicrons. And so if there was some consideration what to put in it but that actually would be the broadest if there's going to be an Omicron variant that is circulating.

I think it's going to be a global issue, and

so doing that would actually help our -- you know, help the whole global conversation. I think that all of these considerations should be brought forward together. It's clear that immunity is waning, and so therefore we're going to need boosters. And so the consideration needs to be what that should look like, and I think that's going to be important moving forward. Thank you.

DR. ARNOLD MONTO: Thank you, Dr. Gans. Dr. Pergam and then Dr. Wharton. Dr. Bernstein is next after that.

DR. STEVEN PERGAM: Thanks, Dr. Monto. I think for me the crux of this is really the last question because the discussion above is various considerations of updating the vaccine strain composition. But I think really the question is do we update the booster and do we update the primary vaccine series. That to me feels like a fundamental question and something that I think is challenging.

DR. ARNOLD MONTO: Steve, the problem is -- the problem is our voting question which we're leading up to --

DR. STEVEN PERGAM: I agree.

DR. ARNOLD MONTO: -- is only the booster.

DR. STEVEN PERGAM: Right. I understand, and I think we can focus on the boosters today. But I think this is going to keep coming back as a question, and part of the reason that's true is that what we've seen at least for boosters is we've seen booster data with different doses than what we're seeing in primary vaccine series. And I think what's going to be critical for us as we're thinking about these changes is how we're going to be approaching this in the future because what we're seeing right now is, you know, good responses with doses that are different than what we're getting with the ancestral strain versus the Omicron strain.

I think in Moderna it's 25 and 25, and then Pfizer is 15 and 15 or 30 and 30. So it's a difference -- and we're comparing sort of apples and oranges here. So I just want to make sure that when we get to this question we talk about this more -- that that becomes a fundamental piece because boosters aren't available everywhere. And if we are making major changes to

this, it's going to be a -- it's going to have global effects on how we're approaching vaccines in general.

DR. ARNOLD MONTO: Yeah. I think we needed a day or so more for this meeting, but besides everything else because there are --

DR. STEVEN PERGAM: I totally agree with you. I think that's kind of more my point.

DR. ARNOLD MONTO: -- because there are multiple -- one thing we might want to do is while discussing the issue of boosters, which is going to be our voting question, talk a little bit about if you can broaden your thought processes and talk about single versus bivalent boosters because that's been something -- another confusing topic that's been brought up. So we might want to think about that as we go through this because it has issues in terms of the dose and all sorts of things, questions that have already been raised. I think Dr. Bernstein is next, followed by Dr. Wharton.

DR. HENRY BERNSTEIN: Thank you, Dr. Monto. I had a couple questions. One of them is assuming T cell immunity is important for vaccine effectiveness, why

isn't it measured routinely in these studies?

DR. ARNOLD MONTO: Having done population-based studies I know one of the answers in terms of the way collection has to occur, but do -- Dr. Weir?

DR. JERRY WEIR: So there have been measures of T cell immunity. The problem is of course it's even harder than antibody to both standardize those measurements and decide which measurement actually relates to something clinically. They're just very hard things to do, and I think if you turned it back and said we want every manufacturer to measure a T cell response, you'd get some measurements.

But I think you would just have a composite of apples and oranges measurement. So it's very difficult to pin down what type of T cell measurement is meaningful in the -- as far as protection. Again, I think the field all agrees that cellular immunity is important, but how you measure it and how you correlate it to protection is very difficult, even more so than antibodies.

DR. HENRY BERNSTEIN: Thanks. That's too bad. I think it would be really important.

DR. JERRY WEIR: It doesn't mean -- I'm sorry, let me finish. It doesn't mean that everybody's not interested in it, and there's a lot of people in different places, not only companies, are pursuing it. And I think that will be one of the challenges going forward is you pursue this. You come up with standardized measurements. You find out what is really the most relevant thing you should be measuring, and so yes, there's still a lot of interest and a lot of work going on.

DR. HENRY BERNSTEIN: I think that would be incredibly helpful. A second question I have is I was confused by the time required to produce a vaccine strain change, whether it's an mRNA platform or the protein subunit platform. I thought one manufacturer said they could have vaccine by July, and then I thought I heard the FDA -- maybe it was Dr. Marks -- say that we're talking a few months.

DR. ARNOLD MONTO: Dr. Marks, we have a lot of population to vaccinate.

DR. PETER MARKS: I actually think it would be very helpful if we could ask each of the manufacturers

when they will have vaccine available of these various sorts. I think I could say this for each of these, for the two mRNA and for the protein-based vaccine, but it might be helpful for each of them to state when they might have vaccine available, even assuming -- it just might be helpful to have them state this. It does take two to three months for the manufacturer of these mRNA vaccines closer to three months I believe, but I'd rather here it from them rather than from me.

DR. ARNOLD MONTO: This is to a different variant than we have currently.

DR. PETER MARKS: That's correct because they have to make a template. They make a DNA template which then allows them to produce the RNA, et cetera, so it does -- they do have to -- it does take some time here. At least in some cases that's how they do it, but they have to make -- they have to take the steps to make the different variant vaccines.

DR. ARNOLD MONTO: And is this to either a bivalent or a monovalent?

DR. PETER MARKS: I believe from the standpoint of the manufacturers, but let's get them to

answer.

DR. ARNOLD MONTO: Okay.

DR. PETER MARKS: I believe that in this case it's not like a bioreactor where I believe in this case it may not be that much more complex for them between the two differences, but let's get them to answer.

MR. MICHAEL KAWCZYNSKI: Dr. Monto, we do have Moderna's hand up. Do you want me to go to each one of them?

DR. ARNOLD MONTO: Okay. Go ahead.

MR. MICHAEL KAWCZYNSKI: Okay. We'll start with them, and then --

DR. ARNOLD MONTO: You handle this. I can't do it.

MR. MICHAEL KAWCZYNSKI: Yeah, quite right. All right. I'll help you out here. Okay. Moderna, take it away.

DR. STEPHEN HOGE: First on the question I heard earlier on bivalent vaccines --

DR. ARNOLD MONTO: We can't hear you.

MR. MICHAEL KAWCZYNSKI: Here. I'm going to boost him up. Go ahead. I'm going to turn up his

volume. Go ahead, sir.

DR. STEPHEN HOGE: Can you hear me now?

MR. MICHAEL KAWCZYNSKI: Yes.

DR. ARNOLD MONTO: Yes, we can hear you.

DR. STEPHEN HOGE: Great. So first on the question of the bivalent Omicron containing vaccine we will have hundreds of millions of doses in August and September for global supply. We've been manufacturing that at risk throughout, and so that would be available starting July and August. I think that was the question.

The second part of the question I heard from Dr. Marks was related to if we did a strain update, and so while we'll have a couple hundred million doses available in August and September, if we were to make a decision right now to switch over to a BA4/BA5 containing vaccine it would take us about three months to conduct the manufacturing processes and prepare the submissions to the FDA, again, assuming no clinical data requirement, no data to assess the vaccine at all. And if we did that, we would have that available and assuming a rapid review cycle sometime in late October

or early November at large scale and, again, be able to produce similar amounts of that vaccine.

Again, that assumes that we would be facing BA4/BA5 in November. What we know is we're facing BA4/BA5 right now in August and September, and we do believe we have a vaccine that can help address that.

DR. ARNOLD MONTO: And if we wanted a monovalent BA1 vaccine.

DR. STEPHEN HOGE: So a monovalent BA1 vaccine, we have the BA1 vaccine as a part of the bivalent, and so it would go a little bit faster than the BA4/5 timelines I have right now. We have been studying that in clinical trials and could prepare those submissions. I wouldn't want to -- I would want to spend a little bit more time thinking about what it would take to switch because we do believe the bivalent platform has demonstrated superior durability, sorry.

DR. ARNOLD MONTO: Right. It's in between the two predictions.

DR. STEPHEN HOGE: Correct.

DR. ARNOLD MONTO: Okay. Thank you. Who's next, Mike?

MR. MICHAEL KAWCZYNSKI: All right. Next we will go with Pfizer. All right. They have their hand up next, so Pfizer, get ready here.

DR. KATHERINE JANSEN: Yeah, hello. I'm Katherine Jansen, head of vaccine research and development at Pfizer. So as to the question of vaccine supply, regardless if you want to look at a BA1 containing or a BA4/5 containing vaccines, we are prepared -- Pfizer BioNTech is prepared to satisfy all of our contractual obligations, those that are currently existing and future ones, in the United States, and we already have produced significant numbers of a BA1 modified Omicron vaccine.

And we are in the process of producing large numbers of a BA4/5 modified Omicron vaccine that is available for roll out, pending of course regulatory -- that there's an agreement on the regulatory pathway and there's an agreement on which vaccine is recommended for the United States in the first week of October. Thank you.

DR. ARNOLD MONTO: Thank you. And Novavax?

MR. MICHAEL KAWCZYNSKI: Hold on. It must

mean it's Gregory?

DR. GREGORY GLENN: Yep, yes. Can you hear me?

MR. MICHAEL KAWCZYNSKI: Yeah, we can hear you. There you go. Let's turn that light on. There you go. Now we can see you. Go ahead.

DR. GREGORY GLENN: Yeah. Just, I mean, as noted by earlier manufacturers we have begun work at risk in this, you know -- and that does include both the BA1 and BA5. And as you know, you know, we've been setting up our manufacturing network, and I think we in part have been awaiting the decision here today we have BA5 to made to scale and BA1 being made at scale. And, you know, we're kind of waiting on the decision here, but we think it depends on the requirements and clinical data.

Obviously we have BA1 in the clinics, and we expect that data taken September. If there's a requirement for clinical data, you know, that would be important for us to know. BA5 or BA1, we think we could supply it by fourth quarter if that's needed. Although I hope you saw we made a strong case for the

deployment of our prototype vaccines, especially the booster set which really does describe pretty much everyone out there, even if they've been infected or immunized.

So we would like to put out there that the prototype with our technology seems to give very broad antibodies, and then of course that would help. You know, sticking with the theme that we have currently, you know, it would be a preference, but we definitely are as we said working on BA5 and BA1 and wait for I think guidance on whether there's going to be a requirement for clinical data to support the specific variant deployment. It would be helpful for us to know.

DR. ARNOLD MONTO: Thank you. Thank you all. Dr. Wharton, followed by Dr. Levy.

MR. MICHAEL KAWCZYNSKI: We want to let Dr. Marks make a comment first.

DR. ARNOLD MONTO: Okay. Dr. Marks first.

DR. PETER MARKS: You know, I think just for our Novavax colleagues I think it's really important for us to try to understand -- in terms of a booster I

think we understand that it will be a ways off here. In terms of availability we have not given an emergency use authorization yet, but I think it also -- it behooves us to understand when the vaccine might be available if the company's willing to discuss that were an emergency use authorization to be granted.

DR. ARNOLD MONTO: Is the company going to respond? I guess we're getting -- I guess Novavax is not going to respond to the -- were you asking a question, Dr. Marks, of Novavax?

DR. PETER MARKS: I think Dr. Gregory is back for us now. Thank you.

DR. ARNOLD MONTO: Okay. He's there. All right. Okay, Greg.

DR. GREGORY GLENN: We had a little trouble with the set up here. So could you repeat the question? I was off audio for just a second.

DR. PETER MARKS: Dr. Gregory, I think the question here is that we noted that although an emergency use has not yet been granted by FDA I think the question was would -- pending an emergency use authorization from FDA, when would your prototype

vaccine, your current vaccine be available for distribution in the United States?

DR. GREGORY GLENN: I think our target is quarter four, so, you know, this year sometime between October and December.

DR. PETER MARKS: That would be for -- I believe you're answering for an updated vaccine. We're talking about the current version of the vaccine.

DR. GREGORY GLENN: Oh, thank you. Yes, I think this is July, so once EUA's granted our vaccine should be available in July, the prototype Wuhan vaccine.

DR. ARNOLD MONTO: How many doses?

DR. PETER MARKS: Thanks.

DR. ARNOLD MONTO: How many doses would that be, Greg?

DR. GREGORY GLENN: You know, I'd have to get back to you, but, you know --

DR. ARNOLD MONTO: Just a ballpark.

DR. GREGORY GLENN: Well, the contract is I would say as many as needed, so the U.S. government has the contract who would buy it, so as many as needed.

We have a lot of doses available, and, you know, once EUA's granted we're ready -- very eager to get those doses released.

DR. ARNOLD MONTO: Thank you.

MR. MICHAEL KAWCZYNSKI: All right. We're back on. Yep. Thank you. I was going to say let's get Dr. Wharton back up here, and now just as a reminder we do have a lot of hands up. So I think we've got about 10 or 12 hands up.

DR. ARNOLD MONTO: Dr. Wharton.

DR. MELINDA WHARTON: Thank you. So the virus has demonstrated that it's clearly continuing to evolve, and as it evolves it's leading to immunization. We can't develop, authorize, and deploy an updated vaccine in time to prevent an impending wave based on match, and we can't predict which of the many variants that are circulating may emerge as our next wave. So we really do need vaccines that provide broader protection against the variants that haven't yet emerged, and for that reason I think based on current evidence that we could get broader protection with the booster that included an Omicron strain. And so I'm

supportive of that.

DR. ARNOLD MONTO: Thank you. Dr. Levy, followed by Dr. Sawyer.

DR. OFER LEVY: Hi. I wanted to make -- I'm sorry, can you see me and hear me?

DR. ARNOLD MONTO: We can hear you. We can't see you.

DR. OFER LEVY: Hi there. I wanted to make a statement again about correlates of protection. I would like to hear from FDA what their overall approach will be in the coming year around improving our understanding of correlates of protection. We spend a good amount of time reviewing antibody data. We have no doubt that antibodies are important, and yet for all the antibody data we have, we don't have a level of antibody that anybody is comfortable stating is a correlate of protection.

So yes, the antibodies are important, but so are the T cells. We heard from Dr. Weir, yes, T cell assays are trickier. They're more diverse, but it's not going to happen without federal leadership to have a standardization of a T cell assay and encourage or in

fact require the sponsors to gather that information.

So what is the effort to standardize the preclinical assays? This is an effort that's critical not just now but for future cycles of vaccine revision. If we aren't able to define a correlate of protection, we're fighting with one arm tied behind our backs. And for the preclinical data on mice, are assays standardized? Do we (Audio skip)? And then there can be species specificity, so what about preclinical human in vitro models? So I'd be eager to hear from FDA about these topics.

DR. ARNOLD MONTO: Dr. Weir.

DR. PETER MARKS: This is Peter Marks. Maybe I'll take this one.

DR. ARNOLD MONTO: Okay. Go ahead.

DR. PETER MARKS: The issue of this is -- I mean, Dr. Levy brings up an incredibly important point that T cell mediated immunity is very important here. It is just -- it was difficult to study initially. It's not for a lack of understanding of the importance here. We have been having conversations with our colleagues at NIH and throughout government about how

we might move forward here.

It's something that we don't have an answer to yet, but it is something, Dr. Levy, we are pursuing and continuing to pursue for how we move forward because obviously as we develop vaccines in the future it will become ever more important because we won't be able to have a large naïve population to vaccinate with newer vaccines. And we will need to understand the T cell response better, so I take your point. It's just we haven't solved the problem yet.

While I have the floor for a moment, Dr. Monto, we have been able to extend the time here if we need it. We will be able to go until 5:30. I hope we don't need to, but if we need to, we can. And I would really strong suggest to us as a committee that we try to rigorously go down and go through the questions and try to talk through some of the responses here because it really will help us to have some discussion of BA1 versus BA4/5 and some discussion of a monovalent versus bivalent.

I think the question of what we do to the primary series, we'd love to have some discussion of

that. That's probably not quite as important, but at least the questions one through three here I think would be really nice to be able to try to work through. Over. Thank you.

DR. ARNOLD MONTO: Dr. Marks, we have ten hands raised right now. Just do the math in terms of how much time it will take just to go through the discussion right now. I can't force people to answer the later questions when they want to have comments about the first question. I've tried to broaden the --

DR. PETER MARKS: Let's just make sure we work through them.

DR. ARNOLD MONTO: -- include bivalent or monovalent, which I think is an important one. I'm not sure we can address the BA1 versus BA4/5 today. I hope we can, and I'll do my best. But it's up to the Committee to decide what they're going to be talking about, and when we have ten people who want to make comments, we can't force the agenda. So having said that and got that off my chest, Dr. Sawyer, followed by Dr. Berger.

DR. MARK SAWYER: Thank you, Dr. Monto. You

know, I am in favor of a strain composition at this time. I think we're all troubled by the steady erosion of immune protection at least as measured by antibody that we've seen and the requirement for more and more boosters.

It's been pointed out several times that we lack cellular immunity data, but it seems to me that with the ability of this virus to mutate eventually we're going to have vaccines that do not protect against severe disease. And although it's been pointed out that the current Omicron related strains are less severe in general, even a less severe strain if it's more transmissible can lead to more death just because of the shear number of people who get infected. So I think given that speed of evolution we're going to be behind the eight ball if we wait longer.

As it was pointed out in the public comment that the public perception is that FDA is already delaying approvals, and I think we have enough data here presented today to move forward with the strain change. I've not heard much downside to going to a bivalent vaccine that includes Omicron related strains

other than the theoretical concern that a new strain might change the side effect profile, but we're unlikely to learn that in clinical trials. We're only going to learn that when the vaccine is rolled out to large numbers of people.

So I'm in favor of a strain change. I'm in favor of a bivalent vaccine. I'm persuaded by the argument that a monovalent might be risky. Dr. Marks' invitation, I would say that a BA1 variant is sufficient and probably will happen faster than a BA4/5, and I can't -- and I'm willing to extrapolate clinical date for all ages based on the immune response data that we've heard. Thank you.

DR. ARNOLD MONTO: Thank you, Dr. Sawyer, and you've given exemplary comment because you tried to comment on more than the first item in the discussion questions because that's what we're going to need to do if we're going to be able to get through this before 7:00 at night. Dr. Berger.

DR. ADAM BERGER: Okay. Thanks. And I definitely appreciate the directive to try and address some of the other points here. You know, I think much

of what I have to say has already been said. It definitely teaches me to raise my hand earlier, especially with this group.

But I want to come back to some of the points we made back in April, and I'm not sure that -- rather I should say it's unclear that we can or should treat COVID as we do flu. You know, I think the mutation rate being so much higher than flue is at this point means that we likely aren't going to get ahead of picking a specific sublineage, so I actually do agree with where WHO came out and others have stated before that search for something that provides broader protection is likely to be better in this scenario.

The good thing, though, is that we actually do have a very highly effective vaccine right now, even with Omicron being present, as long as people are actually getting boosted. You know, there is obviously concern about waning going on, and I do have concerns about the clinical meaningfulness of the titer data as well as the long term durability that we currently don't have a lot of data to support. So it sounds -- in terms of overall support I think I do support the

idea of considering a strain change.

I'm not sure that if I answer the first question it's necessary at this time, and this time is June 28th. And part of this going back to what I originally stated is we don't know what the variant of the day is going to be when we get to the end of the year or next year, but we might want to be able to be prepared for it. And so answering the question at this time I'm not sure that we have evidence to support a change necessarily today.

The thing that really impressed me with the Novavax data -- and I do understand that it hasn't been reviewed -- is it really spoke to the idea that there isn't a one size fit all answer to whether or not a strain change is necessary or going to be necessary. And I do recognize that they don't have an EUA for the booster at this point, but, you know, thinking ahead to what we're going to be asked or what the answers to what we give today will be, it does speak to the idea that perhaps the question we have to vote on actually needs to be narrowed specifically to address mRNA vaccines that have current approval for booster usage

as opposed to being a broader conceptualization that it has right now.

I mean, in many ways I think the answer could be very platform specific depending on what we're actually being asked to look at, and I think in terms of the selection of a specific sublineage, you know, I do think that the ones that are going to be further away are going to be the ones that are going to be better to select. At this point in time based on the data -- and I'm trying to answer some of these questions -- if we did vote for something related to mRNA, I would support something that would go along the lines of BA1.

Whether there's a requirement for a bivalent vaccine versus a monovalent vaccine, I take it so broadly that there isn't -- the data doesn't support using a monovalent as the primary end booster, and so in that regard I think we are talking about only looking at a booster following a primary that is going to be taken up by the prototype strain. And so in that case, you know, the data doesn't support or doesn't speak against using a bivalent vaccine in that regard.

Although I do see some differences in Pfizer and Moderna based on whether or not the bivalent is going to be better than the monovalent depending on which one we're talking about. So I suppose --

DR. ARNOLD MONTO: We're talking about the bivalent booster after a primary series.

DR. ADAM BERGER: Right. Yes, I agree. So that's where I think if we were talking about something, I think that's the only point that we'd be getting towards is using a bivalent for a booster dose and not alone. So, you know, what I'd like to see additional data on, you know, I really do think we need to have a better understanding of the clinical meaningfulness, the impact on severe outcomes and disease. And I'd like to have some further data on the long term durability of any type of change in the actual vaccine composition, so I'll end there. Thanks.

DR. ARNOLD MONTO: Thank you. Dr. Marks, could we have further clarification of FDA's view of efficacy -- current efficacy or efficacy that you're -- or effectiveness against (Inaudible). Were you able to hear that? There was a -- there was an interruption on

my call.

MR. MICHAEL KAWCZYNSKI: Yeah, that was weird.

DR. ARNOLD MONTO: But Dr. Marks, could you make a comment about prevention of hospitalization and severe disease and where we are in terms of waning and the necessity for boosters? Because I think that's what -- I've heard comments suggesting that boosters -- mRNA boosters are not going to be necessary, so we don't have to worry about the composition.

DR. PETER MARKS: So I would put up the slide here from the beginning. I do think that we have to make sure that we're being accurate as to taking the totality of the data that was presented by CDC, and I guess my CDC colleagues could come back and correct me if I'm wrong about anything I will say now. We do know from data in Israel, data in the United States that after two doses of vaccines immunity against these variants is clearly waning the time.

Remember, we only have half of our population boosted; right? So half of people -- more than half in the United States have only received two doses, and therefore their ability to be protected against Omicron

-- the current Omicron has waned itself. And even those who have received three and four boosters, we know that after three -- sorry, three or four doses, I shouldn't have said boosters -- three or four doses, that after three doses of vaccine or one booster we know from this data now from Israel and from the United States that particularly in older individuals, those 60 and up, that protection wanes with time. And that translates into increased risk of death, which is shown to be reduced by additional booster doses.

Now, I think we also understand that from a standpoint of public health we can't be giving boosters left and right, so it was felt that thinking about a booster campaign towards the fall based on the modeling data that you were shown earlier today whether it be given a little earlier or a little later would help us protect the population against potential additional waves. And the thought was that you would potentially want to best match the strain that -- even if you don't match the strain, you would want to start with a strain that was furthest evolved at this time to which the current vaccine was least effective. And that's why

the focus on the BA4/5 data, which the current vaccine does the least to prevent.

So I think I would perhaps take issue with saying the BA1 was the furthest removed and perhaps say that BA4/5 might be because the current vaccines have the least effectiveness -- at least appear to have the least effectiveness against BA4/5. And you saw some data presented on that, and that would be -- and that's not just the data you saw today. There's additional data out of South Africa that also corroborates that.

So I think the goal from today is to try to come up with what would be the right composition, and I think the supposition we're making here is this would be for a deployment sometime this fall. I know we heard about deploying a vaccine right now against Omicron, but it would seem that right now while we're at this plateau I'm not sure that this is the point at which it would be deployed. It may be that it would be deployed with this fall booster campaign in order to best protect us against what may come during this coming winter. Over.

DR. ARNOLD MONTO: And we do hear a difference

of opinion between Dr. Subbarao representing WHO that has talked about BA1 being by antigenic cartography further away and the occurrence of disease in South Africa where the decrease in effectiveness against severe disease seems to be greatest with 4/5. Am I correct in that?

DR. PETER MARKS: That does appear to be correct, and I believe the data that we're seeing is that it looks like both -- again, from data that we're aware that BA4/5 may produce a good immune response both in animals and in humans from natural infection that will help protect against BA1.

DR. ARNOLD MONTO: And not the reverse?

DR. PETER MARKS: That's correct. BA1, if you look at the data that was shown by the different sponsors -- and we can bring that up again -- BA1 does not neutralize -- depending on Moderna's data or Pfizer's data it's anywhere from threefold to fivefold lower neutralization against BA4/5 than against BA1, at least for the current vaccine. And it would appear that even for a BA1 there is a -- that there is that reduction, and perhaps, Jerry, could you help me out

here? Because I think you --

DR. ARNOLD MONTO: And I don't want to get hooked on the sublineage issue because basically you all can look at this as time evolves. Part of the problem here is that a decision needs to -- a recommendation from the VRBPAC needs to be made sooner rather than later because the time availability of the vaccine. So Jerry?

DR. JERRY WEIR: Yeah. A couple of comments if I can keep them straight. One is back to, Arnold, you mentioned the antigenically distant according to cartography. It is true that on the cartography BA1 looks a little further away, but BA4/5 is also quite a ways away on that cartograph thing if you're just looking at that. It's also true you have to put that into context. BA4/5 together as well as BA2.12.1 are still much closer to BA2 than they are to BA1, which is really nowhere right now.

So I think you have to look at the whole picture, not just one thing like antigenic cartography. But even if you just look at the antigenic cartography, BA4 is a long way away antigenically from Wuhan

Washington just like BA1 is. Now I forgot the other thing, Peter, you mentioned.

DR. ARNOLD MONTO: If I can interrupt, that's not something --

DR. JERRY WEIR: Sure.

DR. ARNOLD MONTO: -- that we have to vote on today.

DR. JERRY WEIR: No, no, no. I was just trying to point out that --

DR. ARNOLD MONTO: It's something that we need -- okay.

DR. JERRY WEIR: I was just trying to point out that --

DR. ARNOLD MONTO: Right, I get it.

DR. JERRY WEIR: -- Subbarao mentioned that when you pinned her down she said she would take something antigenically as far away, and I'm just saying that BA4 is also pretty far away. Okay. And Dr. Marks mentioned something about boosting, so when I tried to show a couple of examples about virus boosting -- and again, caveat, virus is not the same as vaccination -- it does seem like a boost of any kind of

Omicron broadens the response. And I think that's what WHO also thought is that boosting of Omicron by any exposure will broaden the antibody response, but there is data that suggests -- and Dr. Marks mentioned this, that we've seen this.

It's unpublished, but at least you have to -- once you see it, you remember it -- is that subsequent infection by BA4/5 seems to broaden even more than subsequent infection by BA1 or BA2. I think that's what you were asking, right, Dr. Marks?

DR. PETER MARKS: That's exactly correct.

DR. JERRY WEIR: Okay.

DR. ARNOLD MONTO: Okay. Thank you all. Now we'll try to move on. Dr. Perlman, followed by Dr. Reingold.

DR. STANLEY PERLMAN: Yes, thank you. So I was going to make several points, some of which were just discussed. So in terms of the bivalent question of vaccines, I'm a fan of a bivalent vaccine because I think that the original vaccine has done so well. So if one was going to choose a bivalent -- a monovalent versus bivalent, I would go for the bivalent.

I'd also go for the BA4/5 for the reasons that Dr. Weir and Dr. Marks just said. The BA4/5 are really the derivatives of BA2, much more than they are of BA1. So if BA1 is actually antigenically different -- I've heard some people say that BA2 is -- BA4/5 particularly, but BA2 as well are almost as distant from BA1 as they are from the original variants. The second point is that multiple both anecdotal and other discussions of how people are getting infected with BA4/5 after having been infected with BA1, so the protection of BA1 is not so great. So that's what puts me more towards a BA4/5 containing vaccine.

The other thing is that my impression is BA4/5 has picked up some of the mutations nearer to -- even though it's quite antigenically distant, it's picked up some of the mutations that were found in some of the original strains so that how the virus is evolving is not totally clear. And then the very last point I wanted to make was that -- so I would come down on a bivalent vaccine with the BA4/5 and the original prototypic strain. But the one thing I'm really concerned about is worldwide will this fly?

And I'm uncomfortable with having U.S. as it were first -- having a vaccine that's not accessible to the rest of the world is one of the problems already politically in the world is that people think that the U.S. and other rich countries put themselves first. And if we're saying that a bivalent vaccine is so much better but it's not accessible to much of the world, I think that's ultimately a bad thing for getting vaccines out to the whole world. So that's all I was going to say.

DR. ARNOLD MONTO: Thank you, Dr. Perlman. Dr. Reingold followed by Dr. Cohn.

DR. ARTHUR REINGOLD: Thanks, Arnold. So, you know, midway through the morning I was definitely leaning towards updating the composition of the vaccine and including an Omicron variant, and I still lean in that direction. But, you know, I do need to point out another difference between this virus and flu or the vaccines. Each year when all the smart people decide what goes into flu vaccine all the old flu vaccine disappears, and we really only have one new flu vaccine except for the high potency for old people versus

regular potency. But we already have quite a profusion of different COVID vaccines that providers are struggling with.

So I do worry about implementation issues if we have both a monovalent vaccine for the initial series and then a bivalent vaccine for the boosters. We haven't heard much about these vaccines in children, but we already know that the various dosages for children certainly pose a number of different implementation issues around the vials, the tops of the vials, the colors. So I do worry about having one vaccine for a primary series and a different vaccine for a booster just in terms of implementation, confusion, storage, a whole host of other implementation issues. Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Cohn, followed by Dr. Lee.

DR. AMANDA COHN: Thanks. So I just wanted to add a couple of additional thoughts. I think most of what I was thinking has already been said. I think I do support a strain change for potential boosters that would be used in the fall. I think what Dr. Marks said

around we're seeing waning in older adults is really important. I'm not sure for example that I think everybody will need a booster dose in the fall, but I think if people are going to be recommended for a booster dose -- and it is likely that older adults will need one -- then I would support the strain change to a bivalent vaccine.

I don't think we should lose the prototype. I think it's a known entity, and it's doing really well in its current job. And we don't know what the next strain will look like, so I don't see any risk in keeping it bivalent. So I think that would be really important.

B4/5 seems like the right way to go. I'm still a little bit hesitant or confused about the difference in the number of weeks or months that that would take to produce BA4/5 compared to BA1, but I think regardless if you're talking about boosting in October the BA1 was circulating last December. So the amount of time between when you're actually boosting and when that strain was circulating, it just feels like given all of the things that FDA has said and

where we think -- and additional changes that will occur and the number of people who were infected with BA1, that BA4/5 is the ideal choice, especially if it can be given or produced as quickly as possible.

DR. ARNOLD MONTO: Dr. Lee, followed by Dr. Chatterjee.

DR. JEANNETTE YEN LEE: Yes. So I think one of the concerns I have is that I'm supportive of the strain change, but all of our discussion really honestly and all the data we've seen on boosters on this strain really is in adults. And I think the greatest concern has been about the waning immunity in adults. What I don't know that we've address and we're probably not going to address it today is how we are going to extrapolate this information for the children.

We don't know the waning immunity. We don't have a lot of information on it, but we need to, I think, think about modeling or something like that because as we know the youngest group just got approved a year and a half after the original approval in December of 2020. And my concern is that if we don't have a strategy they will always be behind in terms of

the fact that the virus is evolving and they would never be necessarily getting vaccinated against the most recent strain. So I hope at some point we will be able to have a discussion on that on how that will happen because I don't think it's that straightforward for the reasons I just stated. Thank you.

DR. ARNOLD MONTO: And, Dr. Lee, I don't think this is the last time we're going to be meeting about some of these questions. Dr. Chatterjee, followed by Dr. Bernstein.

DR. ARCHANA CHATTERJEE: Hello. Yes, thank you, Dr. Monto. I'm going to be very brief just to try and answer the questions that are listed. So I'll start with the first one, which is the selection of a different strain to perhaps add to the prototype, and I think this is needed -- one of the things that we saw data on but we really haven't focused much on is the increase in hospitalizations that's happening. So in terms of severe disease we are seeing breakthrough severe disease in people who are vaccinated with the prototype strain, so I think that that is a strong argument to say we should be thinking about adding to

the strain composition.

In terms of the specific sublineage, it sounded like at least one of the manufacturers has a supply of BA1 available, so should that become necessary to deploy it seems like that could be deployed pretty quickly. I am in support of developing a bivalent vaccine containing the prototype plus perhaps the BA4/5 because that would be the latest variant that is out there that we would need protection against.

And finally the point I'll make about -- two points actually. One is with regard to the implementation question that was brought up, I believe, by Dr. Reingold, that if we have a separate vaccine for boosters versus a primary series, that is has the potential for causing confusion and errors. And so that's something that we have to keep in mind, and then the last point with regard to what Dr. Lee just said, I've asked the question several times today actually, asking for pediatric data. And basically the response has been well, we don't have any, and I think that that is an inadequate response at this point in time. In

terms of extrapolating available data, I am very hesitant to extrapolate that from adults into children, and I think the pediatric studies need to be done. And they need to be done now.

DR. ARNOLD MONTO: Thank you, Dr. Chatterjee. A point of information, Dr. Weir or Dr. Marks, if this is -- if the bivalent vaccine that we've heard about is not the ancestral strain, is it? I thought it was beta.

DR. JERRY WEIR: No.

DR. ARNOLD MONTO: It's the ancestral strain?

DR. PETER MARKS: Any of the bivalents we'll be talking about will be the prototype vaccine, not beta. Prototype plus an Omicron component.

DR. ARNOLD MONTO: Okay. Because some of the data will be -- some of the data that was prototype.

DR. PETER MARKS: Right. I know.

DR. JERRY WEIR: You're right.

DR. PETER MARKS: It was confusing. It was confusing.

DR. ARNOLD MONTO: Okay. I just want to unconfuse myself because -- so it's ancestral plus an

Omicron that we're talking about.

DR. JERRY WEIR: That's what we're talking about, yes.

DR. ARNOLD MONTO: Okay. Now, Dr. Bernstein, followed by Dr. Nelson.

DR. HENRY BERNSTEIN: Thank you, Dr. Monto. So I'm stuck at the very first question. Is a change to the current COVID-19 vaccine strain composition necessary at this time? And the reason I'm struggling is that at our April meeting -- and then it was reiterated well by Dr. Weir today -- the strain change requirements should be, one, data driven, and it seems to me that the data that's been presented today seems quite limited, especially for BA4 and BA5. The second requirement was that the evidence shows that the current vaccine strains are not effective versus severe disease, and it appears to me that the ancestral strain, the current vaccine, is effective against severe disease.

And then the third requirement is that the evidence is compelling that a new vaccine with a strain change would have improved vaccine effectiveness, and I

don't think we really have the data to be able to say that, although we looked at immune response. But we really don't have it relating to vaccine effectiveness. So in sum, I think including an Omicron strain in the vaccine seems to have some potential, but the data, especially for BA4 and BA5, are limited at this time. So that's why I'm struggling to even make a strain change at this time.

DR. PETER MARKS: Dr. Monto, can I make a comment?

DR. ARNOLD MONTO: Yes. Yes, Dr. Marks.

DR. PETER MARKS: So I really appreciate -- Dr. Bernstein, I really appreciate your comment, but this is why I opened my comments today by saying this is truly a challenge. And it is science at its hardest because I believe as was perhaps alluded to in the open public hearing we have to make a decision to wait until the evidence is irrefutable that we need a change, at which point we may have had this variant pass on and we'll have something else here. Or we'll have to feel comfortable based on what we've seen with previous variants because the manufacturers as was noted by one

of them have already -- each of them have had experience with making other variant vaccines. Each of them have seen immune responses that are robust developed against them.

Each of them has seen safety in several hundred people through these different variants. Do we take that experience combined with what we know to be a totality of evidence that indicates that the current vaccines are no longer quite as protective against severe disease, particularly in older individuals, but probably also tailing off into younger individuals if you look at the VA data, granted, much less so -- and that as we've seen the evolution to BA1 and now BA4/5, that becomes even more accentuated? I think that's what is at the heart here of the discussion.

DR. HENRY BERNSTEIN: Thank you. Are you then suggesting that the vaccine composition strain change might be a BA4 and BA5 as opposed to a BA1 which we currently have? And if it was needed in July, it sounds like Moderna has that because I don't know that that's as important as -- when BA4 and 5 are more than 50 percent of the circulating strains.

DR. PETER MARKS: I think for purposes of discussion today -- and let me try to simplify something. Both manufacturers at risk have told us today that they've made BA1 vaccine, whether it be bivalent or monovalent, so I think were we to see a major wave in BA4/5 -- sorry, a major wave in BA4/5 or that we needed to deal with something right now because the wave was going up very quickly, we could potentially deploy one of those vaccines. It would not necessarily be optimal for longer term protection.

I think for the purposes of our discussion right now we should perhaps make the assumption that we will not need to deploy or we're not worried about that deployment but we are worried about or concerned about what we might deploy if we were able to deploy something in October or November during which time we would be able to manufacture -- or have the manufacturing of a new strain composition. Does that seem reasonable? I think that's just able to focus things a little bit better here because I think the question of what we do for a BA1 if we had to deploy it is one that will depend on the epidemiology, and that

product actually exists now.

DR. ARNOLD MONTO: And the voting question as it currently exists is Omicron.

DR. PETER MARKS: Correct. Do we include an Omicron component? But it does not note whether it should be a monovalent or a bivalent.

DR. ARNOLD MONTO: Okay.

DR. PETER MARKS: We were hoping to have that information from -- what we're hearing here is -- what I've heard so far is some preference for a bivalent vaccine because it maintains the presence of this prototype vaccine which we seem to have a lot of comfort in and confidence in with good reason, and so that's what I've heard so far. I haven't yet heard somebody make a strong case for either a monovalent BA1 or BA4/5, but I'd love to hear -- I'm saying that to draw out anyone who would like to make that case.

DR. ARNOLD MONTO: Well, I'll bring up one issue that would be the case if we go for a bivalent vaccine containing the ancestral strain plus an Omicron, and that is we are going to be limited in the quantity of the Omicron component given the fact that

we can't go above a certain microgram level because of side effects. And I'm not sure we've seen direct comparisons of this in terms of antibody levels, assuming that antibodies are not a correlate but sort of correlate with protection. Dr. Weir.

DR. JERRY WEIR: You hit another nail on the head. You saw one piece of data that spoke to that, and that's all. You did see a piece of data from Pfizer that did compare bivalence to monovalence at different doses in the same population in the same study. Again, limited but that's what you had. And that's why I tried to point that out, that there did seem to be in that one study some sort of dose response. And so yes, that is why we were throwing this out there to try to get the opinions of you and the rest of the Committee.

DR. ARNOLD MONTO: Which is why I am not enthusiastic about a bivalent vaccine if the ancestral strain will never reappear again and we're going in a certain direction. Next one is Dr. Nelson, followed by Dr. Meissner.

DR. MICHAEL NELSON: Thank you, Dr. Monto, and

thank you, Dr. Marks, for that lead in. I had some of the same concerns about the two scenarios, and in fact addressing the question of necessity, I was really struck by your remarks about the confluence of risks that will occur this fall. So could we possibly wait based on the evidence before us? Probably. Should we wait? I really don't think so.

I think with the waning vaccine efficacy and the confluence of risks this fall we need to make a move sooner rather than later and direct our sponsors in the proper direction. I'm not going to take the bite on a monovalent shift to a vaccine. I'm actually in the bivalent camp to be perfectly honest, Dr. Monto, so I have some questions regarding the immune response that's occurring to these bivalent vaccines. I'm not sure we've teased out exactly what's happening at the cellular and humoral level. What I can't tell is whether the immune response is really related to conserve portions of the added variants or indeed new epitope responses from the inclusion of the bivalent vaccine, and the risks that would occur in going to a monovalent vaccine is the latter.

If the true breadth and durability response is due to the new valence responses, does that need a prime boost and subsequent doses to really see the vaccine efficacy? So some additional data that would tease out the proportion of the immune responses related to new epitopes from the variants would be very helpful. We're certainly not going to have that data any time soon or be able to make a nimble judgment on how to reconstruct these vaccines based on that type of data, but that's why I would favor of a bivalent vaccine.

I think that you're going to get some immune response on a dose level, even from the conserved portions of the variants that will contribute. I think it is the affinity maturation from the repeated doses of third and fourth exposures that are leading to the increased efficacy in boost in titers that we're seeing.

Now, I did want to touch on finally the challenging our immunobridging approach for younger children, so I agree whole heartedly with Dr. Lee. She beat me to the punch. I'm worried about our younger

age groups always being behind the power curve in receiving updated vaccines, so I don't know what the right strategy is. But the current one of sequential immunobridging is probably not the right one, and we do need to do some concurrent dose response and safety studies in children to accelerate that schedule and accelerate their access to the vaccines. Thank you, Dr. Monto.

Dr. ARNOLD MONTO: Thank you, Dr. Nelson. As usual you've hit a number of topics very squarely. As somebody who has worked for many years with influenza with repeat vaccinations there are a number of questions that we're going to have to watch or issues that we're going to have to watch as we repeatedly vaccinate. Dr. Meissner, followed by Dr. Pergam.

DR. CODY MEISSNER: Thank you, Dr. Monto. I had been thinking that the archival D614G strain should be in the future vaccines based on the remarkable success that these vaccines have had. Although Dr. Monto's comment gives me pause as someone who's had so much experience with these vaccines. I certainly take his thoughts seriously, but I think -- so I think we

should use this archival strain.

And I had thought we would use one of the new Omicron strains in it, but I think I just wanted to point out one fact. That is regardless of what vaccine's used, I think we've seen there's going to be waning immunity, and it's unlikely to last very long. If this coronavirus becomes seasonal like the well-known coronaviruses, then it will be much easier. If this virus continues to cause disease throughout the year, it's going to be a difficult challenge because how many boosters is too much, is too many?

I remember Sara Oliver gave a very nice presentation at an ACIP meeting a couple of months ago, and I think it was in April. And she spoke about immune tolerance and imprinting and potential problems. Now, there's no evidence of that now, but if we get to the point of administering too many boosters, I worry that we could begin to see some untoward side effects and in particular in children. And I think, again, I think we have to be careful about the issue of myocarditis.

With a bivalent vaccine we'll be making

additional antibodies, and if it is the molecular mimicry issue or even if it's just an immune reaction to the messenger RNA vaccine itself that's causing the myocarditis I think we want to be sure that that's not becoming an increasing problem in children. So it seems to me that until more data does become available I think if the decision is to proceed with a bivalent vaccine it should probably be directed initially at adults rather than at children while we work out not only the dosage but potential side effects. Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Pergam, followed by Dr. Levy.

DR. STEVEN PERGAM: Thanks, Arnold. Yeah, this has been great listening to other's opinions on this because there's some diversity in thought, so I thought I would just comment on the questions ahead of us. I think at this point we know that the ancestral strain has waning immunity. I think concerns about increasing hospitalizations in Europe and South Africa does suggest that we need to add to the strain composition, so I think that first question to me feels like a yes.

I think depending on the lineage -- and I sort of agree with others that BA4/BA5 would be ideal, and the comments by Dr. Marks are helpful because if we do see large changes in the short term that we have, the BA1 is a fall back as an option. But I think currently continuing forward for BA4/BA5 would make sense.

I'm with others. I'm not with you, Arnold, on this, I'm sorry. But I think the bivalent remains intriguing to me partially because of something that Dr. Gans pointed out is I like the fact that it does appear to have prolonged efficacy compared to the monovalent. And I like that as potentially extend the period of time when boosting has to happen, and then I think for children it gets really complex. But I think this is a reminder -- and I could be wrong about this, and maybe Dr. Marks or others can comment.

But my understanding at least from discussion was Moderna had a study that was ongoing in their cohort of individuals that they did for primary vaccine series where they were doing booster dosing with a Wuhan strain or a Washington strain boost and a bivalent boost for children. And I was hoping that

maybe they could give us an update about when that data may be available because that could be quite important in terms of talking about what this looks like in the future for children specifically.

DR. ARNOLD MONTO: I don't know whether we want to go back to the sponsor, but Dr. Weir, Dr. Marks, can you answer?

DR. PETER MARKS: Dr. Monto, I think it probably would be best to go back to the sponsor, Moderna, on that one for them to --

DR. ARNOLD MONTO: Okay. We can go to the sponsor.

DR. PETER MARKS: I'm sorry. I don't want to misspeak for them.

DR. STEPHEN HOGE: We are currently conducting both primary series and booster studies in both infants and the pediatric population, and we will have data in October from those studies -- October and November.

DR. ARNOLD MONTO: And what are -- what's in the vaccine?

DR. STEVEN PERGAM: It's BA1, correct?

DR. STEPHEN HOGE: That's with the Omicron

containing BA1 bivalent.

DR. ARNOLD MONTO: Bivalent with what -- what is the second strain?

DR. STEPHEN HOGE: It's an ancestral -- it's prototype plus bivalent BA1.

DR. ARNOLD MONTO: Okay. Thank you. Okay. Dr. Levy, followed by Dr. Gans.

DR. OFER LEVY: Yes, hi. You know, I was reflecting on the first question that's asked of us, and really in thinking about it, it seems to me a better question or maybe a more appropriate question is that with respect to the potential change in strain composition for the fall, do the benefits outweigh the risks of making (audio skip) based on the limited information we have in front of us today? So that's kind of how I'm thinking about it, and I just wanted to put that out there because I was thinking about Dr. Bernstein's critique that with respect to the initial parameters that were laid out by VRBPAC maybe we didn't get all those.

But it seems to me that this is really a benefit to risk ratio, and it's a time sensitive

situation. So that's one construct that might be helpful to people. The other I wanted to endorse what Dr. Chatterjee said about the bioethics here, the presumption of inclusion of children, so I wanted to add my voice to that and encourage FDA to encourage the sponsors in that regard.

And then finally, there'll be a big focus on safety just like Dr. Cody Meissner said, especially the myocarditis. And the query to FDA is we have good safety surveillance in place. What could be done to enhance that in light of a potential change in composition as we head into the (Audio skip)?

DR. PETER MARKS: This is Peter Marks. I'm happy to say that I feel pretty comfortable that the safety surveillance that we have in place currently with the Sentinel BEST system is actually quite good, and in fact there was a paper just published out of our group looking at myocarditis rates using that system, monitoring millions of individuals. So I think that we can get a pretty good sense of things.

I do think we do understand myocarditis a little bit better which is it does seem to have some

relationship to antigenic steroids because this is mainly males. And it peaks in the 16 to 18 year range, and it also seems to have something to do with the inter-dose interval because it does seem to be peaking after the second dose. And there was a lower incidence clearly after the third doses that we've seen.

It's not quite back to the rate after the first, so I think we will have good safety systems in place because we already have them there ready to move here. And in fact we are working to actually build them further by bringing on more states to our surveillance system. There have been some challenges getting some of the immunization information from certain jurisdictions, but we're working through those. And I believe we'll be in a good place here.

DR. OFER LEVY: Thank you, Peter. And what do you think of the construction with the potential benefits of a strain composition change outweigh the risks? Is that a proper way to think about this?

DR. PETER MARKS: I think that's fine. I think what we're looking to -- we're taking -- I think we're taking that to be what the overall conversation

here is, and I take your point. I don't know that we need to change the wording of the question, but I think your point is well taken. And I think we should be transparent about this.

What we're doing today is working in a very challenging area because none of us has a crystal ball. If you do, come over to my house right now. I really would like it, but none of us has a crystal ball. And we are trying to use every last ounce of what we can from predictive modelling and from the data that we have that's emerging to try to get ahead of a virus that has been very crafty.

You know, for something that's only nanometers in size it's pretty darn crafty, and that's what we're trying to do here. So I think what you're saying is -- we take the point that we're trying to make our best judgment here, and that does mean that it's that the benefits outweigh the risks of making this change. Thank you.

DR. ARNOLD MONTO: Yeah. What I say is -- Peter, is that this is a virus that doesn't follow the rules.

DR. PETER MARKS: I agree with you, Dr. Monto.

DR. ARNOLD MONTO: Dr. Gans, followed by Dr. Gellin. The list seems to be getting longer instead of shorter. Dr. Gans.

DR. HAYLEY ALTMAN-GANS: Well, there's so many points that are being raised, but as you know since I was an early one onto this and had responded to some of these questions I continue to think that the important issue and I think where we have been caught several times is that we are behind. And so considering these questions now before there's a need is actually very important, so we can't always wait for the data to catch up. But in the background we would urge our sponsors as well as FDA to continue to complete collecting that information, and one of the most important things if we do come together at any point as our sponsors are submitting their data or any point when we have to consider actually if we want to go with these boosters when they're needed is that we need to see the safety data.

I mean, this is rare moment, and I would agree that our safety systems are so advanced and so great

and really can catch the things that no one can catch in the trials that we would be asking for or anything like that is that that safety data would be the actual billions of doses that have actually gone into people come forward. So we can just have that in context. So we sort of stopped hearing about it a little while ago, and that would be something that I would love to see come forward.

I'm very -- I'm always going to want the children to have the safest available option for them. And that likely is going to be a vaccine to prevent them from getting infected, and so I agree with my colleagues that that needs to come forward. But I'm very -- you know, I'm inspired that our companies are already looking at it.

So we heard from Moderna. They are looking at these. I would remind my colleagues that the doses within those -- and we actually didn't hear about the pediatric dosing, but the doses at least that we heard about today are less than that which is in the primary series and even in the booster of the monovalent. So that's something for us to consider as we're thinking

about sort of this antigenic composition, which I think is very promising. And at least from the Moderna -- I didn't see it detailed as well in the Pfizer data, but that actually seems to boost even the ancestral strain even higher than the monovalent which is a double dose, which is an interesting finding.

I would point out that we just need that information to come forward with us and be able to review at least the safety. And the last, you know -- hopefully as sort of the process moves forward and maybe we have a third vaccine option -- fourth vaccine option for us with Novavax that we really actually also consider a mix and match as we have in the past. I brought that up earlier, but I thought I should bring it up again because if that really does broaden our ability to get to these Omicron and the B4/B5 which is starting to take over faster, then that might be an option also to bridge us. And I think that has been brought up. Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Gellin, followed by Dr. Berger.

DR. BRUCE GELLIN: Thanks a lot. It's late in

the discussion. It's late in the day but late in the discussion, so I'm not going to repeat the many great comments that have been made. I will say that I'm in the bivalent camp with an emphasis that we need to be paying attention to safety as has been reinforced by several who've preceded me. Also we want in the spirit of the Stanley Cup where the puck is going rather than where it's been, so I lean to the BA4/5 as we heard about the potential for having supplies available in the near term.

I also want to reinforce what Dr. Levy brought up before about the central coordination of these studies going forward. I don't know whose job that is in the federal government. I can guess, but I think we need to have better central coordination not just for those studies but what the plan is going forward. Without such a plan we're going to be playing whack a mole as this virus evolves because it's going to continue to evolve. We'll get better at this, but we still need to get ahead of it.

So what we need clearly is a different -- the vaccines we have are miraculous, but they're first

generation vaccines. And we're going to need to have vaccines that are more durable, have broader protection, decreased transmission, and presumably there is a Warp Speed 2.0 that's brewing somewhere. We haven't heard about that, but maybe in our next session we can hear about what the plans are to get ahead of this rather than chasing it. Thanks.

DR. ARNOLD MONTO: Thank you. Dr. Berger, followed by Dr. Sawyer.

DR. ADAM BERGER: Thanks. I just wanted to come back to the BA4/5 versus BA1 discussion just because it sounds like there's a pretty significant lean towards BA4/5. I just want to point out that right now we're not seeing a lot of data that's coming out from a specific Omicron variant sublineage here with 4/5. Most of the data that we've seen has been specifically BA1, so we'd be talking about making a strain change based on essentially just having preclinical data and CMC data. And I'm not sure then I'm as comfortable making that leap without having some type of clinical efficacy, even if it's just the immunogenicity types of studies that have been done at

least on the BA1 data itself.

So I just wanted to put that out there that, you know, if we were talking about making a strain change for this fall and leaping towards a change towards BA4 and 5, we would really be having to do that off of preclinical data only. And, you know, I just wanted to put in the piece to say I think we really do need some clinical data to support it. Thanks.

DR. ARNOLD MONTO: Thank you. Dr. Sawyer, followed by Dr. Offit.

DR. MARK SAWYER: Yeah. Just to follow up on that BA1 versus BA4 and 5 discussion, clearly the majority feel 4/5 is the way to go. We will -- if we make that recommendation, then we need to rely on FDA doing the math, that is the companies are always optimistic and sometimes end up being delayed when they actually can produce a sufficient supply. And I'm hoping the timeframe includes any regulatory time that the FDA will need to approve the new versions because what we don't want is for them to come out too late to address this predicted wave in the fall.

My second quick point is, again, there's

concern about side effects and serious side effects in children. We are unlikely to learn about those during any clinical trial, so I think myocarditis in particular, we're only going to know that when we roll out the vaccine and the safety systems do their review.

DR. ARNOLD MONTO: Yeah. And I'm sure from what I've heard that there's already been discussions as you've heard about the 4/5 issue in terms of supply. Dr. Offit, followed by Dr. Cohn. Or did you take your hand down?

DR. AMANDA COHN: No, no. I just wanted to quickly just add to just remind everyone that the data in the children from 5 to 11 that we have on myocarditis also shows that there's no increase in myocarditis based on the lower -- likely because of both the lower dose they're getting and the age at which they're at as Dr. Marks indicated. But I just want to -- I don't want concerns about myocarditis to increase the amount of time it takes to get a vaccine available to this age group because especially in that younger age group, in that less than six- and five-year-olds, they really still just have a primary series

recommended. And they don't even have that first booster dose, so, you know, I think it's really important that we keep that younger age group as a very distinct group than the group of young male adults who have been shown to be at increased risk for myocarditis.

DR. ARNOLD MONTO: And Dr. Offit.

DR. PAUL OFFIT: Yes. Thank you. First of all, I appreciate all my colleagues' comments. They've sort of helped sharpen what my thinking is here. I think first of all I certainly agree that there is an advantage in a boost in the fall for what is essentially a winter virus but for certain groups, obviously not for everybody. But I think certain high risk groups benefit, and I certainly agree that we need to broaden the immune response once we cross sort of the Rubicon with Omicron and these subvariants that are currently more immune evasive, especially for mild disease.

The question to me is Omicron the right strain. That's where I'm getting hung up here. I think that the -- I agree with Dr. Perlman actually

because I would actually support this, for this to be a BA4/BA5 strain. If I told you that -- what if I told you that the 1.75-fold increase that you see against Omicron with the Omicron boost wasn't clinically significant for the strains that are currently circulating? Or said another way that if Moderna had presented the data showing what their neutralizing antibody response was to BA4/BA5 wasn't any different than what they were seeing with the neutralizing antibodies against -- you know, that were induced by the ancestral strain?

So I'm still not comfortable enough that we have the information that makes us essentially support this new product, and I don't think it's fair to ask people to take a risk, which is true with any vaccine that we get, if we don't feel comfortable with the level of protection that we're likely to get by including Omicron. So thank you.

VOTING AND VOTE EXPLANATION

DR. ARNOLD MONTO: Thank you, Dr. Offit. And

now you're going to have to take such a risk because we have the voting question, and what I'm going to propose is that we go right to the voting question and vote because then we will have time for an explanation of the vote, which will be our next discussion topic and our final discussion topic. So Christina.

MR. MICHAEL KAWCZYNSKI: It's Sussan today. We're having Sussan do the vote, so I'm bringing Sussan in.

DR. ARNOLD MONTO: Oh, okay. Sussan.

DR. SUSSAN PAYDAR: Hi, everyone. Thank you, Dr. Monto. Only our 9 regular members and 12 temporary voting members, a total of 21, will be voting in today's meeting. With regards to the voting process, Dr. Monto will read the final voting question for the record, and afterwards all regular voting members and temporary voting members will cast their vote by selecting one of the voting options, which includes yes, no, or abstain.

You will have two minutes to cast your vote after the question is read. Please note that once you have cast your vote you may change your vote within the

two minute timeframe. However, once the polls have closed all votes will be considered final. Once all of the votes have been placed, we will broadcast the results and read the individual votes aloud for the public record, and at this point I just wanted to ask does anyone have any questions related to the voting process before we begin?

DR. ARNOLD MONTO: I think everybody's done it already once before.

DR. SUSSAN PAYDAR: Everybody has done it already. Okay. Dr. Monto, if you could please read the voting question for the record?

DR. ARNOLD MONTO: Does the Committee recommend the inclusion of a SARS-coV-2 Omicron component for a COVID-19 booster vaccines in the United States?

DR. SUSSAN PAYDAR: Okay. The two minutes are up. It looks like all votes are in. Michael, please end the vote by closing the polls and broadcast the results. Okay. There were 21 total voting members for today. We have 19 who have voted yes, two who have voted no. I'm going to go ahead and read the votes one

by one. Here are the voting responses.

Dr. Adam Berger, yes; Dr. Amanda Cohn, yes; Dr. Archana Chatterjee, yes; Dr. Arnold Monto, yes; Dr. Arthur Reingold, yes; Bruce Gellin, yes; Dr. Cody Meissner, yes; Dr. David Kim, yes; Dr. Hank Bernstein, no; Dr. Hayley Gans, yes; Dr. James Hildreth, yes; Dr. Jeannette Lee, yes; Dr. Mark Sawyer, yes; Dr. Melinda Wharton, yes; Dr. Michael Nelson, yes; Dr. Ofer Levy, yes; Dr. Paul Offit, no; Dr. Randy Hawkins, yes; Dr. Stanley Perlman, yes; Dr. Steven Pergam, yes; Dr. Wayne Marasco, yes. I believe I covered everyone.

That concludes the voting portion for today's meeting. I'll now hand over the meeting to Dr. Monto for asking the Committee for their vote explanation. Thank you, Dr. Monto.

DR. ARNOLD MONTO: Okay. Now, hands raised for explanation of votes. This is voluntary. Whoever wants to explain their votes, please raise your hand. Dr. Cohn is first.

DR. AMANDA COHN: I just wanted to quickly say that I voted yes. That does not mean that I think that -- you know, I do believe strongly that we need to

continue to encourage the companies to collect as much data as possible on the safety and immunogenicity of whatever strain is chosen, and I do hope that it is a bivalent strain. And I also just want to be clear that this doesn't mean that we are -- that we are saying that there will be boosters recommended for everyone in the fall, but my belief is that this gives us the right vaccine in preparation for potential need for boosters in the fall. Thank you.

DR. ARNOLD MONTO: Thank you, Dr. Cohn. Dr. Kim, followed by Dr. Marasco.

DR. DAVID KIM: Thank you very much. You know, given the data, including the safety data, and given that Omicron is antigenically distinct -- what we learned from the prototype strain -- I do think that it makes sense to go with a bivalent vaccine to optimize protection. Again, that's given what we know at the moment, and obviously we're all waiting for additional data to be collected and to be analyzed so that changes, if necessary, can be made.

Now, that said, there are questions on logistics of vaccine production, distribution, and

administration with changes in the vaccine recipe. More impact on viral vector vaccine and protein subunit vaccine are at play here. There are camps of people due to various reasons who are on the fence with the COVID-19 vaccine, and they are holding out for an improved viral vector vaccine or a protein subunit vaccine to enter the stage. And that obviously has an impact on what we have been calling mix and match.

Perhaps it's more of a mix and mix but using various combinations of vaccines that are available to promote protection. And I think this has a -- with this recommendation, how these vaccines are to be used will come into play as far as our strategies to implement the various vaccines that are gonna be available out there. And we're adding to the mix consideration for a bivalent vaccine that takes into account what we have learned so far. So I am happy for this opportunity to proceed with making a decision based on what we know to optimize the protection based on what we know. Thank you.

DR. ARNOLD MONTO: Dr. Marasco, followed by Dr. Levy.

DR. WAYNE MARASCO: Yeah. So, you know, I voted in favor of Omicron booster because I think it's important to broaden immunity. I'm not sure at this point if the data over the next couple months is not going to show that BA4 and 5 peaks. I mean, if the peak is -- if the total wave is three to four months, we may be on the downside by the fall. So I'm not sure, you know, about the 4/5 component versus just an Omicron component, but I will say that I was pretty impressed today that we can do better.

And I'm not sure that mRNA vaccines as they have been presented so far are giving us the best kind of immunity that we can get here, so I think this is a step in the right direction. But we have to reevaluate this as we move forward because I think there's something to be said about, you know, a trans-presentation to be versus a cis. And what I mean by that is antibodies that are elicited to be able to bridge more than one variant to come out, and it may be different for different vaccines. And I think that's what I actually saw today. Thank you.

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

followed by Dr. Gellin.

DR. OFER LEVY: Thank you. I was actually of two minds. You're hearing a lot from a lot of the Committee members a feeling that we would love to have more information, and you could certainly count me on that camp. So I had feedback to FDA about what I think we could be doing better, and I think that's important to improve our process. It's not the last time we face these kind of deliberations, and at the same time we face a time sensitive decision. If we're going to have something better in the fall, the decision has to be made very soon, and so I believe it was more likely than not the benefit outweighed the risk of including an Omicron component. And so I voted yes. Thank you.

DR. ARNOLD MONTO: Dr. Gellin, followed by Dr. Meissner.

DR. BRUCE GELLIN: Thanks. I provided my rationale of how I was going to vote before, so I want to use this just to make a comment. You know, we have been following to some degree the path that the flu vaccine strain selection has given us, recognizing that it's not the same and the speed of mutations makes it

much more problematic. But at a higher level maybe there's an exception, but it seems that in the flu world the FDA conversation which follows the WHO conversation is usually the same.

I'm not sure who takes this one on but should we -- and we weren't asked to vote on sublineage, although we're -- so we're leaving that to the FDA. But we heard a number of people leaning towards the 4/5, and I guess given that the conversation between the regulators and WHO about what the plans are going forward globally, if the recommendations are to make different vaccines -- I'm just highlighting that this a pandemic, and these are global manufacturers. And so we're going to have to think through what the implications are going to be, not only for a potential range of different formulations that Dr. Reingold highlighted but for different formulations of what's included in them around the world. Thanks.

DR. ARNOLD MONTO: Dr. Meissner.

DR. CODY MEISSNER: Thank you. Thank you, Dr. Monto. And if it's appropriate -- and please say if it's not -- but I wondered if Dr. Cohn and Dr. Wharton

could comment on what would be the threshold on which they and the CDC might recommend a booster? And the reason -- in the fall of this new --

DR. ARNOLD MONTO: Why don't we ask Dr. Marks first about that kind of implementation issue? Dr. Marks.

DR. PETER MARKS: Yeah. No, thanks. I think what's going to drive this will be the epidemiology that we see over the coming months, and I think there will be a fair amount of discussion. Right now the critical thing is the manufacturers need to know what to put into their vaccines.

Over the coming months I think we'll get a sense, and there'll be plenty of time for debate over who is most appropriate for boosters. I think as we sit here I take it from the discussion I've heard that it seems like most people would feel -- again, you can correct me if I'm wrong -- that the people who got fourth boosters -- you know, people 50 years and up and certainly 65 and up -- might be appropriate for a booster in the fall. I think there'll be some discussion about boosters for others but remember --

just again I have to remind us all. Half of Americans have not even received a first booster, so that's why this is highly relevant because we're hoping that we can convince people to go get that booster and help mature their immune response and help prevent another wave.

And again, I totally take the point which I've heard that BA4/5 may not be circulating later this fall, but by moving to this either as a bivalent or in some part of the vaccine composition we may at least bring the immune system closer to being able to respond to what's circulating. So I think there'll be continued discussions, Dr. Meissner, and I think I'm happy to have my CDC colleagues comment as well.

DR. CODY MEISSNER: And Dr. Marks, can I also -- and the reason I asked was because there is a financial risk that the pharmaceutical companies are taking by making these vaccines, and if there's a low likelihood that the vaccines would be recommended, then they could incur a significant loss. And so I guess that's the direction I was going in. It may not be answerable.

DR. PETER MARKS: I guess I would say that I would make our recommendations here knowing that the vaccine manufacturers will be kept whole by the United States government for at least some vaccine. I think that's probably a reasonable assumption. I could be wrong, but I think it's a reasonable assumption.

DR. CODY MEISSNER: Thank you.

DR. ARNOLD MONTO: Dr. Reingold. Dr. Reingold has his hand up.

DR. ARTHUR REINGOLD: So I just want to say I concur with the notion that a yes vote was (Inaudible) the likely benefits outweighing the risks. In terms of the implementation issue around boosters I just want to point out again the question of a well of confusion about which vial is what and who should get what when. All those people who are on the fence wanting a booster or a fourth booster and may at this point now be inclined to wait until -- I'll get that bivalent booster instead of the one that's available now. So I think there's a lot of important messaging to do. Thank you.

DR. ARNOLD MONTO: Thank you. And to my

surprise there are no hands raised at the moment, so I'd like to conclude the meeting by saying that I think we have done the best we can in a difficult situation with imperfect data and inability to say what is going to follow what looks like an Omicron 4/5 wave. We've looked at the options that are available and come up with a recommendation and some advice that FDA can follow as we move forward into uncharted territory. Unfortunately looking in the past doesn't help us a great deal to look in the future for this virus which has baffled a lot of us and made predictions almost irrelevant.

So thank you all and I'd like to give the floor over to conclude the meeting first to Dr. Marks and Dr. Weir and then to Prabha for the formal closing. Dr. Marks, Dr. Weir.

DR. PETER MARKS: Dr. Monto, first of all thank you for running this meeting. A challenging meeting run very smoothly here. I just want to make sure that Dr. Weir and I can at least just -- I want to make sure that -- sometimes it's a good practice to repeat back what we hear so we make sure that if any

one of the Committee members feels strongly that maybe have not heard correctly they have the time right now to raise their hand and make sure that they have their voice heard.

So we know the vote. I think from polling around from the notes that I took it seemed like the consensus among those who were for a change was that a BA4/5 to be included was what made sense. It did seem like there was a fair amount of enthusiasm for a bivalent, and I think the bivalent it seems was -- I'm not sure how much of that was based on the data shown on the beta Omicron or how much of that was based on the fact that prototype has done so well and keeping prototype there alongside an Omicron component makes us feel more comfortable. But I'll take it either way unless anyone wants to try to clarify that.

But it did -- the bottom line is it seems like a BA4/5 bivalent was the sense of the Committee. Would be very happy to hear if somebody want to provide some further explanation of why they felt more comfortable if anyone feels like they have any other explanations they'd like to provide for the bivalent nature. And I

think we'll go back and struggle with the issue of what we do about the primary series having heard some of the challenges here about what it would be to operationalize this versus some of the challenges that we might have because of some of the vaccine rollouts that are going on right now.

Does that make sense? I guess from the Committee members I'd be interested, Dr. Monto, just make sure that --

DR. ARNOLD MONTO: That's what I think I heard from the Committee members. Where myself in terms of the bivalent I've gone up and back in terms of which would be preferrable. What I would like to see is a head to head comparison of a bivalent with a monovalent vaccine which we're not going to have in time to roll one or the other out. And it's similar in terms of everything else we've seen.

The BA1 versus BA4/5, I must admit I came in thinking about the BA4/5 was the way to go. Then I heard Dr. Subbarao who has a vast amount of experience working in the flu area coming up with the -- what I forced her to say that BA1 was the way to go. I think

what is critical there is that the vaccine, whatever we have as a booster or whatever we call it in the fall should contain an Omicron, and that was the vote that we took.

Is there anybody -- not to prolong the process, does anybody in the Committee have anything else they want to say beyond that summary? Going once, going twice. We have a volunteer. Dr. Marasco, you will have the final word.

DR. WAYNE MARASCO: Yeah. Dr. Weir and Marks, I was just curious since this got brought up a couple times in the discussion, so in terms of alternatives, I mean, we did hear from Novavax about the potential of their vaccine giving further coverage. But they haven't been granted an EUA, so, I mean, is this going to be in the formula for the fall as well that that vaccine should be available? Or is that beyond what the Committee should be discussing more?

DR. PETER MARKS: I think that, you know, the company said when they thought they would make their -- they would see their vaccine available, and the company replied that they thought they would have availability

of their vaccine in July. I can take the company for their word for that. I can't tell you when we'll take regulatory action, but I think there's some complexities here.

And this is one of those issues where I wish there -- we could be more transparent, but there are certain things that the Trade Secrets Act prevents us from saying in a public venue. And I can't say them in this venue, but you should know that we will not delay making sure that that vaccine is available. Once the vaccine is ready to be available we will make sure that there's no delays.

DR. WAYNE MARASCO: Thank you.

DR. ARNOLD MONTO: Thank you. And Dr. Marks, would you start the closing process? And then we'll give it over to Prabha.

DR. PETER MARKS: Yeah. Dr. Weir, do you want to say anything else here? I just want to make sure that you have a chance just in case because he's the first -- Dr. Weir's the first person I have to thank too.

DR. JERRY WEIR: I wanted to say one or two

things real fast. One is that when we started this a couple of few months ago we all internally recognized that this was an extremely complex set of issues, not just one issue. It was a complex set of issues. When we met in April I think the Committee understood that. Nothing that I heard today changed my mind that it's every bit as complex as we thought it was going in there. And I do think that in spite of the complexity we made a lot of progress, and I also heard what Dr. Marks heard and maybe a few other things that I think we will remember and work on.

I mean, I heard things like the Committee still thinks global coordination is important and we need to figure out something about this going forward. The logistics we know are going to be difficult, and we have to work on that. But I also heard comments about how we still need more information about correlates of protection and the measures of cellular immunity, and so all I can say is we understand this.

And we will just keep working on it as well as working on how to streamline and make this entire process of (Inaudible) opposition better going forward

because you're right. It's not going to be the last time, so anyway, my thanks to everyone that did such a great job. Thank you.

DR. PETER MARKS: So I will begin the close out process here, Dr. Monto. First of all I want to thank the FDA staff, the Advisory Committee staff who as usual has done an incredible job putting this meeting together. They have made sure that it's gone technically incredibly well. Very grateful to the entire Advisory Committee staff and the technical staff working with them.

I also want to thank the FDA staff who did an incredible job, and I need to call out Drs. Weir and Fink who did a lion's share of preparation here as well as the teams. Also want to take a moment to really sincerely thank a number of different presenters today, our open public hearing speakers. We're always open to hearing them, and I appreciate their viewpoints. Also want to thank our CDC colleagues and our WHO colleague for coming and presenting what was very important data as well as the modeling data that was presented.

Also want to thank Novavax, Moderna, and

Pfizer all for their presentations and for really helping to inform us. I'll just take a note that I'm aware this is the last time (Audio skip) --

DR. PRABHAKARA ATREYA: Dr. Marks, you are not -- you're muted. We can't hear you.

MR. MICHAEL KAWCZYNSKI: I turned on your microphone, Dr. Marks. Go ahead. No. Dr. Marks, hold on. His phone disconnected right at the wrong time. Hold on a minute. We're going to disconnect him. That's just sort of funny. We don't want to lose that. Prabha, I'm going to pop you up there. Let Dr. Marks come back in. I'm going to send him the audio. I think he ran out of battery so hold on a second while we get Dr. Marks coming back in and his audio. There he goes. That's what happens -- there you go.

DR. PRABHAKARA ATREYA: Dr. Marks, we couldn't hear the last part of your --

MR. MICHAEL KAWCZYNSKI: He's coming in. There we go. Go ahead, Dr. Marks. You're back. Right at the wrong time. Go ahead.

DR. PETER MARKS: I'm going to back up. Did you hear me start to thank the Advisory Committee

members?

MR. MICHAEL KAWCZYNSKI: Right about there. Yes, you could start there.

DR. PETER MARKS: Great. I'll start right there, and I apologize. I don't know what happened there. I got -- someone booted me off the phone. Maybe I deserved it.

Thank you so much to all the Advisors because what I was saying was that really this is -- I am very grateful for Dr. Monto and for each and every one of you because this is not simple, and a diversity of viewpoints is very important here. And the open dialogue is something that's really important for people to hear. It's important to know that science is not always simple, but we will do our best to work our way through it to make sure that we do our best by public health and the country.

Thank you for all of your input which we will consider very carefully, and we really appreciate the time you spent today. With that, I will turn this over to Prabha. Thank you.

DR. PRABHAKARA ATREYA: Thank you, everyone.

Thank you, Dr. Marks. Thank you, Dr. Monto and all the Committee members and the speakers, for your excellent contributions today. And thank you so much. And with those closing remarks from Dr. Marks and Dr. Weir, I would like to formally adjourn the meeting. It's 5:09 p.m. Eastern Time. Thank you so much and have a good evening. Bye-bye.

MR. MICHAEL KAWCZYNSKI: All right. Thank you, everyone, and with that if you have any questions or comments, please send them to fdaoma@fda.hss.gov. Studio, please take us and clear the feed.

[MEETING ADJOURNED]