# FOOD AND DRUG ADMINISTRATION (FDA)
# Center for Biologics Evaluation and Research (CBER)
# 172nd Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting

## OPEN SESSION

**Web-Conference**
**Silver Spring, Maryland 20993**

**April 6, 2022**

***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 | |
|---|---|
| Arnold Monto, M.D. (Acting Chair) | University of Michigan |
| Paula Annunziato, M.D. (Industry Representative) | Merck |
| CAPT Amanda Cohn, M.D. | Centers for Disease Control and Prevention |
| Hayley Altman-Gans, M.D. | Stanford University Medical Center |
| Adam Berger, Ph.D | National Institute of Health, Bethesda |
| Henry Bernstein, D.D., MHCM, FAAP | Zucker School of Medicine at Hofstra University |
| H. Cody Meissner, M.D. | Tufts University School of Medicine |
| Paul Offit, M.D. | The Children's Hospital of Philadelphia |
| David Kim, M.D., M.A. | U.S. Department of Health and Human Services |
| **TEMPORARY VOTING MEMBERS** | |
| A. Oveta Fuller, Ph.D. | University of Michigan |
| 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. | Boston Children's Hospital 7 Harvard medical School |
| Wayne A. Marasco, M.D., Ph.D. | Dana-Farber Cancer Institute, Harvard Medical School |
| Stanley Perlman, M.D., Ph.D. | University of Iowa |
| Randy Hawkins, M.D. - Acting Consumer Representative | Private Practice, California |
| Eric Rubin, M.D., Ph.D. | Harvard T,H, Chan School of Public Health |
| Mark Sawyer, M.D., F.A.A.P. | University of California at San Diego School of Medicine and Rady Children's Hospital San Diego |

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| Melinda Wharton, M.D, M.P.H. | Centers for Disease Control and Prevention |
| Michael Nelson, M.D., Ph.D. | University of Virginia School of Medicine |
| **SPEAKERS AND GUEST SPEAKERS** | |
| Sharon Alroy-Preis, M.D., MPH, MBA | Ministry of Health, Jerusalem Israel |
| John Beigel, M.D. | NIAID, NIH |
| Trevor Bedford, Ph.D. | Fred Hutchinson Cancer Research Center |
| Robert Johnson, Ph.D. | Biomedical Advanced Research & Development Authority |
| Ruth Link-Gelles, LCDR, Ph.D | Centers for Disease Control and Prevention |
| Ron Milo, Ph.D. | Weisman Institute Rehovot, Israel |
| Ali Mokdad, Ph.D. | University of Washington |
| Christopher Murray, M.D., D.Phil. | University of Washington |
| Heather Scobie,, Ph.D., MPH | Centers for Disease Control & Prevention |
| Kanta Subbarao, M.D., M.P.H. | WHO Collaborating Center for Reference & Research on Influenza, Melbourne, Australia |
| **FDA PARTICIPANTS/SPEAKERS** | |
| Doran Fink, M.D. Ph.D. | Food and Drug Administration |
| Peter W. Marks, M.D., Ph.D. | Food and Drug Administration |
| Jerry Weir, Ph.D. | Food and Drug Administration |
| Celia M. Witten, Ph.D., M.D. | Food and Drug Administration |
| **FDA ADMINISTRATIVE STAFF** | |
| Prabhakara Atreya, Ph.D. | Food and Drug Administration |
| Christina Vert, M. S. | Food and Drug Administration |

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| Lisa Wheeler | Food and Drug Administration |
| Joanne Lipkind, M.S. | Food and Drug Administration |
| Mr. Michael Kawczynski | Food and Drug Administration |

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**OPENING REMARKS: CALL TO ORDER AND WELCOME**

**MR. MICHAEL KAWCZYNSKI:** Good morning. I'm Mike Kawczynski and welcome to the 172nd meeting of the Vaccines and Related Biological Products Advisory Committee Meeting. Throughout today's meeting I may be interjecting at times just to make sure the meeting runs smooth, in case we run into technical issues. I'll be hosting today's meeting. So, this is a full day meeting. We'll roughly end around 5:00 this afternoon. Keep in mind, because it is live, we can run into little issues and may have unscheduled breaks to address that.

With that being said, let's get it kicked off and I'm going to hand it off to our chair, Dr. Arnold Monto. Arnold, are you ready?

**DR. ARNOLD MONTO:** I'm ready. I'd like to welcome everyone -- members, voting members, the speakers who will be joining us during the open public session, and everybody else, to this meeting which is

the 171st (phonetic) meeting of the VRBPAC. The topic today is an open public session to discuss recommendations for COVID vaccines and the booster process, and the process for vaccine strain selection to address current and emerging variants.

So this is a discussion meeting. We are not going to have a vote. This doesn't mean that what we are doing today is not important. We've had two other meetings which were of great importance which didn't result in votes: the one when we affirmed that we needed efficacy studies to license vaccines back -- way back a year and a half ago, another meeting where we discussed the pediatric vaccine program -- again, something which set the tone for the rest of the work on pediatric vaccines.

So today's meeting, looking long-term at what we're going to do to address the threat of COVID-19 as we go forward years from now, is of critical importance in setting the pathway to making choices that will have enormous impact long-term. Saying that, I'd like to turn the meeting over to our Designated Federal

Officer, Prabha Atreya, who will go through the housekeeping items. Prabha.

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

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

**MR. MICHAEL KAWCZYNSKI** Yes, Prabha, take it away.

**DR. PRABHAKARA ATREYA:** Okay. Thank you. Good morning, everyone. This is Dr. Prabha Atreya, and it is my great honor to serve as the Designated Federal Officer, that is DFO, for today's 172nd Vaccines and Related Biological Products Advisory Committee. On behalf of the FDA, the Center for Biologics Evaluation and Research, and our VRCPAC committee, I'm happy to welcome everyone to today's virtual meeting.

Today the Committee will meet in open session to discuss considerations for COVID-19 vaccine booster doses and the process for COVID-19 vaccine strain

selection to address (audio skip) current and emerging variants. Today's meeting and the topic were announced in the Federal Register notice that was published on March 22nd, 2022.

At this time I would like to introduce and acknowledge the excellent contributions of the staff and the great team I have in my division in preparing for today's meeting. Ms. Christina Vert is my co-DFO providing excellent support in all aspects of preparing for and connecting this meeting. Other staff who contributed significantly are Ms. Joanne Lipkind, Ms. Karen Thomas, and Ms. Lisa Wheeler, who also provided excellent administration support. I would like to express our sincere appreciation to Mr. Mike Kawczynski in facilitating this meeting today.

Also, our sincere gratitude goes to many CBER and FDA staff working hard behind the scenes trying to ensure that today's virtual meeting will also be a successful one like all the previous VRBPAC meetings on the COVID topics. Please direct any press or media questions to -- for today's meeting to FDA's Office of

Media Affairs at fdaoma@fda.hhs.gov. The transcriptionist for today's meeting is Ms. Linda Giles.

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

**DR. ARNOLD MONTO:** Yes, good morning again. I'm Arnold Monto. I am at the University of Michigan School of Public Health in the Department of Epidemiology where I study vaccines, specifically influenza and now COVID vaccines, and we work on the evaluation of these vaccines and look at transmission of the infectious agents in human populations. Thank you.

**DR. PRABHAKARA ATREYA:** Thank you, Dr. Monto.

Next, Dr. Hayley Gans.

**DR. HAYLEY ALTMAN-GANS:** Good morning. I am Dr. Hayley Gans, pediatric infectious disease at Stanford University. And I study the immune response of vaccines in many different hosts, including children and immunocompromised. Thank you.

**DR. PRABHAKARA ATREYA:** Thank you. Next, Dr. Annunziato.

**DR. PAULA ANNUNZIATO:** Good Morning. I'm Paula Annunziato. My day role, so to say, is to lead vaccine global clinical development at Merck, and I'm here today as the non-voting industry representative.

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

**DR. ADAM BERGER:** Hi. I'm Adam Berger. I'm the director of the Division of Clinical and Healthcare Research Policy at NIH. I oversee all of our clinical research policy, everything from human subject's protections all through our clinical trial policies.

**DR. PRABHAKARA ATREYA:** Thank you. Next, Dr. Henry Bernstein.

**DR. HENRY BERNSTEIN:** (Audio skip) pediatrics at (audio skip). Hi. I'm Henry Bernstein.

**DR. PRABHAKARA ATREYA:** You are breaking up. Go ahead, please.

**DR. HENRY BERNSTEIN:** Can you hear me now?

**DR. PRABHAKARA ATREYA:** Yes, yes.

**DR. HENRY BERNSTEIN:** Good morning. I'm -- my name's Hank Bernstein. I'm a professor of pediatrics at Tucker School of Medicine. I'm a general pediatrician with a special interest in infectious diseases and vaccines.

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

**DR. AMANDA COHN:** Good morning. I'm Dr. Amanda Cohn at the Centers for Disease Control and Prevention. I'm a pediatrician with expertise in public health and vaccine policy.

**DR. PRABHAKARA ATREYA:** Okay. Thank you. Next, Dr. David Kim.

**DR. DAVID KIM:** Good morning. This is David Kim with the Division of Vaccines in the Office of

Infectious Disease and HIV/AIDS Policy under the Office of the Assistant Secretary for Health. And I am the director of the division, and we work on administering the national vaccine program. Thank you.

**DR. PRABHAKARA ATREYA:** Thank you. Next up is Paul Offit.

**DR. PAUL OFFIT:** Good morning. My name's Paul Offit. I'm a professor of pediatrics at the Children's Hospital of Philadelphia in the University of Pennsylvania a School of Medicine, and my interests are in pediatric infectious diseases and mucosal vaccines. Thank you.

**DR. PRABHAKARA ATREYA:** Thank you. Next, Dr. Rubin.

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

**DR. PRABHAKARA ATREYA:** Thank you. Next, we will do the roll call of the Temporary Voting Members.

**DR. OVETA FULLER:** (Audio skip).

**DR. PRABHAKARA ATREYA:** Thank you. Next, Dr. Randy Hawkins.

**DR. RANDY HAWKINS:** Hi, good morning. Dr. Randy Hawkins, I'm an internist and pulmonary physician, consumer representative, Charles Drew University and in private practice.

**DR. PRABHAKARA ATREYA:** Thank you. Next, Dr. Hildreth -- James Hildreth.

**DR. JAMES HILDRETH:** Good morning. Good morning, I'm James Hildreth. I'm the president and CEO Meharry Medical College, Professor of Internal Medicine, immunologist by training. And I study the pathogenisis of major human viruses such as HIV and SARS-CoV-2. Thank you.

**DR. PRABHAKARA ATREYA:** Thank you. Next, Dr. Jeanette Lee.

**DR. JEANETTE LEE:** Good morning. My name is Jeanette Lee, and I'm with the Winthrop A. Rockefeller Cancer Institute at the University of Arkansas for Medical Sciences. My area is multi-center clinical trials. Thank you.

**DR. PRABHAKARA ATREYA:** Thank you. Next, Dr. Ofer Levy.

**DR. OFER LEVY:** Hi, good morning. My name is Ofer Levy. I'm a physician scientist at Boston Children's Hospital where I'm a pediatric infectious disease attending and Professor of Pediatrics at Harvard Medical School. I direct the precision vaccines program that uses multi-disciplinary approaches to apply precision medicine principles to vaccine discovery and development.

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

**DR. WAYNE MARASCO:** Good morning. This is Wayne Marasco. I'm a professor of cancer immunology and AIDS at Dana-Farber Cancer Institute and Professor of Medicine at Harvard Medical School. I study emerging infectious diseases and in particular host-microbe interactions and antibody responses. Thank you.

**DR. PRABHAKARA ATREYA:** Thank you. Next, Dr. Cody Meissner.

**DR. CODY MEISSNER:** Good morning. Good morning. My name is Cody Meissner. I am a professor of pediatrics with an interest in infectious diseases, particularly viruses and immunizations. And I appreciate the opportunity to participate this morning.

**DR. PRABHAKARA ATREYA:** Thank you. Dr. Michael Nelson.

**DR. MICHAEL NELSON:** Dr. Mike Nelson. I'm Professor of Medicine and Chief of Asthma, Allergy, and Immunology at the University of Virginia. Also a retired Army medical (audio skip) with a longstanding interest in vaccine immune response and (audio skip).

**DR. PRABHAKARA ATREYA:** Thank you, Dr. Nelson. Next, Dr. Stanley Perlman.

**DR. STANLEY PERLMAN:** Good morning. I am Dr. Stanley Perlman from the University of Iowa. I'm a professor of microbiology and immunology and of pediatric infectious diseases, and I have a long-term interest in coronaviruses.

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

**DR. MARK SAWYER:** Good morning. This is Mark Sawyer. I am a professor of pediatric infectious disease at UC San Diego and Rady Children's Hospital in San Diego, and my -- I work in the area of public health implementation of vaccine policy.

**DR. PRABHAKARA ATREYA:** Thank you. Last but not least, Dr. Melinda Wharton.

**DR. MELINDA WHARTON:** Good morning. I'm Melinda Wharton. I'm an adult infectious disease physician at the Centers for Infectious Disease Control and Prevention where I work on vaccines, vaccine programs, and vaccine policy. Thank you.

**DR. PRABHAKARA ATREYA:** Thank you so much. Now I will proceed with the reading of the conflicts of interest statement for the public record. Thank you. The Food and Drug Administration is convening virtually today, April 6th, 2022, for the 172nd 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 April 6th, 2022, the Committee will meet in open session to discuss considerations for use of COVID-19 vaccine booster doses and the process for COVID-19 vaccine strain selection to address current and emerging virus variants. This topic is determined to be a particular matter of general applicability, and as such the meeting does not focus its discussion on any particular product, but instead focuses on the classes of products under discussion.

Therefore, please note that this VRBPAC meeting is not being convened to make specific recommendations that may potentially impact any specific party, entity, individual, or form in a unique way and any discussion of individual products will only be to serve as examples of the product class. Additionally, this meeting of the VRBPAC will not involve approval or disapproval, labeling requirements, go to marketing requirements, or related issues regarding the legal status of any specific products.

With the exception of industry representative

members, all standing and temporary voting members of the VRBPAC are appointed Special Government Employees, SGEs, or Regular Government Employees, RGEs, from other agencies and are subjected to further conflict of interest laws and regulations. The following information on the status of this Committee's compliance with federal ethics and conflict of interest laws including, but not limited to, 18 United States Code Section 208, is being provided to participants in today's meeting and to the public.

Related to the discussions at this meeting, all members -- Regular Government Employees and Special Government Employee 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 purpose of 18 U.S. Code 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts and grants, cooperative research and development agreements or CRADAs, teaching, speaking, 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 the federal ethics and conflict of interest laws.

Under 18 U.S. Code Section 208 Congress has authorized the 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 a special government employee's services outweighs the potential for the conflict of interest created by the financial interest involved or when the interest of 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 that 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 a temporary voting members: Dr. Oveta Fuller, Dr. Randy Hawkins, Dr. James Hildreth, Dr. Jeanette Lee, Dr. Ofer Levy, Dr. Wayne Marasco, Dr. Cody Meissner, Dr. Michael Nelson, Dr. Stanley Perlman, Dr. Mark Sawyer, and Dr. Melinda Wharton. Among these consultants, Dr. James Hildreth, a special government employee, has been issued a waiver for his participation in today's meeting. The waiver was posted on the FDA website for public disclosure.

Dr. Paula Annunziato of Merck will serve as the industry representative for today's meeting. Industry representatives are not appointed as special government employees and serve only 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 alternative or temporary consumer representative for this Committee meeting. Consumer representatives are

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

In addition to FDA staff presentations, we have a large number of other federal and non-federal speakers, as well as some international guest speakers today making various presentations on timely and relevant topics. The following speakers and guest speakers for this meeting have been screened for their conflicts of interest and cleared to participate as speakers for today's meeting.

The speakers include Dr. Ruth Link-Gelles, Program Lead of COVID Vaccine Effectiveness Epidemiology Task Force at CDC and Dr. Heather Scobie, Deputy Team Lead Surveillance and Analytics Epidemiology Task Force COVID-19 Emergency Task Force, also at the CDC; Dr. John Beigel, Associate Director for Clinical Research in the Division of Microbiology and Infectious Diseases, NIAID, NIH; Dr. Robert Johnson, Deputy Assistant Secretary Director of Medical Countermeasure Programs at BARDA in Washington, D.C.;

and Dr. Trevor Bedford who's a Professor at Fred Hutchinson Cancer Research Institute and also investigator at Howard Hughes Medical Institute in Seattle, Washington; Dr. Ali Mokdad, a Professor Health Metrics Sciences at the University of Washington, Seattle; and Dr. Christopher Murray, a professor of Health Metrics Sciences, Director, Institute for Health Metrics and Evaluation, University of Washington.

Additionally, we also have the following international guest speakers: Dr. Kanta Subbarao. She is Director WHO Collaborating Center for Reference and Research on Influenza, Doherty Institute for Infection and Immunity Melbourne, Australia. And we are also joined by Dr. Sharon Alroy-Preis. She is the Director of Public Health, Ministry of Health at Jerusalem, Israel; and last, but not least Dr. Ron Milo, a Professor in the Department of Plant and Environmental Sciences. He is also Dean of Education, Weisman Institute, Rehovot, Israel. We thank them all for their time in making today's presentation.

Disclosure of conflicts of interest for

speakers and guest speakers follows applicable federal laws, regulations, and FDA guidance. FDA encourages all meeting participants, including open public hearing speakers, to advise the Committee of any financial relationships that they may have with any affected firms, its products, or if known, its direct competitors. We would like to remind the standing and temporary members that if the discussions involve any of the products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to inform me, the DFO, and exclude themselves from the discussion, and their exclusion will be noted for the record.

This concludes my reading of the conflict of interest statement for the public record. At this time, I would like to hand over the meeting back to our Chair, Dr. Monto. Thank you, and Dr. Monto, take it away.

**DR. ARNOLD MONTO:** Thank you, Prabha. At this point it is my pleasure to introduce the director of the Center, Dr. Peter Marks, who will give us his

introductory remarks and I'm sure give us a warm welcome.

**FDA INTRODUCTION**

**DR. PETER MARKS:** Thanks very much, Dr. Monto. And indeed, I want to welcome everyone and thank everyone for joining the meeting today. Although we've seen a major decline in the number of COVID-19 cases in the country, the virus continues to circulate and all evidence points to the fact that it will continue to do so and will potentially cause waves of an increased number of cases at points in the future.

This is particularly of concern as we head into the coming fall and winter season. At that point, there may be a confluence of at least three factors that come together to put us at risk of another major wave. First, the immunity of the population against SARS Coronavirus-2, the virus that causes COVID-19, will be waning, particularly in those who were previously uninfected -- sorry, previously infected and not vaccinated and those who received primary

vaccinations but were never boosted.

Second, the virus, which has shown its ability to change over time to evade our immune systems, will have had at least six more months to further evolve. And third, we'll be entering the colder season of the year in which much of the country goes inside, and that's what respiratory viruses tend to peak.

All that taken together makes us conclude that a general discussion of booster vaccination to prevent COVID-19 is warranted at this time so that we can potentially intervene if it's thought to be warranted to make a difference. So that will be the topic for discussion today in a general sense. We're not going to get down to specifics of the exact vaccine composition nor the exact timing, but we'd like to hear the Committee's thoughts on this.

And so, what we'll be doing is having a variety of presentations relevant to the board discussion of boosters. And the goal will be for the Committee to have a general discussion of the principles behind the potential need and timing of

booster vaccination and then how the varying composition of such a booster vaccine should be selected or what principles we might follow. So we really look forward to a productive dialogue today, and I want to thank you, once again, for joining. And I'll now turn the meeting over to Dr. Doran Fink.

**COVID-19 VACCINES:**

**FRAMEWORK FOR FUTURE DECISIONS ON STRAIN COMPOSITION AND USE OF ADDITIONAL BOOSTER DOSES**

**DR. DORAN FINK:** Hi, good morning. I don't think I'm in presenter mode. And so I'll either need to be put into presenter mode, or I'll need someone to advance my slides for me. Thank you.

**MR. MICHAEL KAWCZYNSKI:** You should have the rights now, Doran.

**DR. DORAN FINK:** Gotcha. All right. So good morning, everybody. I'm going to be presenting an introduction to today's topic on COVID-19 vaccines which will be the framework for future decisions on

strain composition and use of additional booster doses. I think my presentation will echo much of what Dr. Marks said in his remarks, but perhaps in a little bit more detail.

By way of background, everybody is aware of the numbers associated with the SARS-CoV-2 pandemic, but I will repeat them here just to remind everyone. Since the beginning of the pandemic in early 2020, SARS-CoV-2 has caused nearly half a billion reported cases of COVID-19 and over six million deaths worldwide. And in the United States we've had nearly 80 million reported cases and nearly one million reported deaths.

As Dr. Marks alluded to, surges in SARS-CoV-2 transmission and surges in COVID-19 cases, hospitalizations, and deaths have been associated with a number of factors. Some of these factors are related to human behavior and include the typical seasonal variation associated with respiratory virus epidemiology and also a variable implementation of public health control measures such as mask wearing,

social distancing, and other measures.

There are factors that are intrinsically related to the biological characteristics of the SARS-CoV-2 virus that have also attributed to these surges. And what we have seen is the emergence of variants, for example, Beta, Delta, and most recently Omicron, that compared to previously circulating strains have been some combination of more infectious, more virulent, and/or more resistant to natural or vaccine elicited immunity.

At this time, we have three COVID-19 vaccines which have emergency use authorization, two of these have FDA licensure for use in the U.S. The various authorized or approved uses of these vaccines are detailed in the briefing document that we provided to Committee members and published ahead of the meeting. I am not going to take additional time to go over these details, but if the Committee needs a reminder, I do have an extra slide at the end that I can go over, if needed.

The effectiveness of available COVID-19

vaccines has been demonstrated both in clinical trials and in post-authorization and post-licensure observational studies. Despite the very high level of effectiveness against disease of any severity that has been observed in randomized clinical trials, we have seen evidence of waning vaccine effectiveness which has been impacted by, again, a number of factors.

First of all, we have evidence to suggest waning protection over time, most notably against milder disease but also to some extent and, especially in more highly susceptible populations, against more severe or more serious COVID-19 associated outcomes. And then intrinsic biological and antigenic characteristics of the SARS-CoV-2 variants that have become dominant have also resulted, as I mentioned earlier, in at least some level of antigenic escape from vaccine elicited immunity. And this has also contributed to vaccine effectiveness that we've observed in post-authorization and post-licensure settings that is less than what we've seen in the randomized clinical trials against -- valuating

effectiveness against the original Wuhan strain.

So while currently available vaccines are not well matched to the dominant circulating variant, which is the Omicron BA.2 sublineage, we do still have some residual vaccine effectiveness. And effectiveness against COVID-19 of any severity as well as in particular more serious outcomes is improved by use of booster doses. And we have very good data to support this conclusion.

We all struggle with the unpredictability that has defined the SARS-CoV-2 pandemic to date. But despite this unpredictability, we need to plan for the future. And these planning efforts for future utilization for COVID-19 vaccine should consider several things; first, whether vaccine strain composition should be modified to improve protection against currently circulating virus and/or to improve breadth of coverage so that vaccines will be more likely to remain effective against potentially emerging variants in the future; and secondly, whether additional booster doses should be recommended in

anticipation of the next potential COVID-19 surge -- and if additional booster doses are to be recommended, then when, and in which populations.

The decisions on these planning questions should ideally be guided by a data driven, formal, transparent, and coordinated process that include all key stakeholders. Additionally, decisions should result in recommendations that are sensible, practical, and understandable.

By sensible, I mean the recommendation makes sense based not only on the data evaluated but also the situational context in which the data are considered. By practical, I mean that the recommendation should be actionable and achievable within the operational parameters of vaccination program. And by understandable, I mean the what and the why of the recommendation to be readily apparent to patients, healthcare providers, and state and local public health authorities which is critical to achieving buy-in and to avoiding confusion.

We all recognize how challenging it has been

to consistently hit on all of these objectives while synthesizing rapidly emerging and evolving data time and time again to make the best decisions possible in the interest of public health. The purpose of this meeting, then, is the lay the groundwork for the decisions that will have to be made in the near and not so near future.

To help guide the discussion today we have a packed agenda of nine presentations that will address key questions related to these future decisions on COVID-19 vaccine strain composition and utilization of additional booster doses. First up, we will have a presentation from Heather Scobie from the Centers for Disease Control and Prevention updating us on the epidemiology of SARS-CoV-2 strain.

Second, we will have another presentation from Ruth Link-Gelles, also from CDC, summarizing what we know about COVID-19 vaccine effectiveness for available vaccines in children and adults. We will then hear from Sharon Alroy-Preis from the Israeli Ministry of Health and Ron Milo from the Weizmann Institute of

Science in Israel about their experience using a fourth dose of the Pfizer vaccine BNT162b2 in the setting of the Omicron surge that occurred in Israel.

After that, we will hear from John Beigel at NIAID about the SARS-CoV-2 antigenic space, and Trevor Bedford from the Fred Hutchinson Cancer Research Center about continuing SARS-CoV-2 evolution under population immune pressure. These presentations will help to inform how data modeling might help to predict antigenic evolution of SARS-CoV-2 and effectiveness of SARS -- of COVID-19 vaccines going forward.

We'll then have another talk that focuses on data and modeling, this time how can data and modeling can help predict the trajectory of the pandemic going forward. This will be an update from the Institute for Health Metrics and Evaluation at the University of Washington given by Christopher Murray and Ali Mokdad.

We'll then end the presentation agenda with a series of three talks, the first being from Kanta Subbarao from WHO. She will give details on the Technical Advisory Group on COVID-19 vaccine

composition which will inform what plans are being considered for how COVID-19 vaccine strain composition decisions might be coordinated globally. We'll then hear about considerations for timelines for development and evaluation of modified COVID-19 vaccines in a presentation given by Robert Johnson from BARDA.

And then finally, we will have our FDA presentation given by Jerry Weir that will consider questions about how FDA should approach future regulatory decisions on COVID-19 vaccine strain composition and authorization of additional booster doses. And more specifically, he will talk about our model -- our established model for strain selection for seasonable influenza vaccines and how that might be applicable or not to the situation that we have now with COVID-19 vaccines.

Following these scheduled presentations and an open public hearing, the VRBPAC will be asked to discuss and provide input on a wide range of topics. We know that this is a hefty slate of questions for the VRBPAC to discuss. We've allotted two and a half hours

for you to do so. And as a reminder -- this has been mentioned several times -- none of these questions re voting questions; they are all general discussion questions. So first and foremost, we would like the Committee to discuss what considerations should inform strain composition decisions to ensure that available COVID-19 vaccines continue to meet public health needs.

And some of the considerations that we would like the Committee to discuss include, but are not, of course, necessarily limited to: first, the role of VRBPAC and the FDA in coordinating the strain composition decisions; number two, the timelines needed to implement strain composition updates; and number three, harmonization of strain composition across available vaccines. All of these will be important factors to consider in the decision process for COVID-19 vaccine strain composition.

Next, we would like the Committee to discuss how often the adequacy of strain composition for available vaccines should be assessed. Thirdly, we would like the Committee to discuss what conditions

would indicate need for updated COVID-19 vaccine strain composition and also what data would be needed to support a decision on a strain composition update.

And then finally, again, in anticipation of a potential surge in the fall or winter which may be with a virus that is antigenically similar to what's circulating now or may be what -- a virus that is very antigenically different, we would like the Committee to discuss what consideration should guide the timing and populations for use of additional COVID-19 vaccine booster doses.

You'll get to see these questions at least several times more as a reminder to help guide your thought process as you listen to the presentations and prepare for the discussion this afternoon. That's the end of my presentation. Thank you.

**DR. ARNOLD MONTO:** Thank you, doctor --

**MR. MICHAEL KAWCZYNSKI:** Okay. Looks like we have about five minutes for a Q&A.

**DR. ARNOLD MONTO:** Okay. Thank you, Dr. Fink and Dr. Marks. Before we go into a few minutes of

questions from the group, I'd like to get your feeling about the granularity of the responses that you -- we are to make. Some of the questions are very specific. How often should the adequacy of the strain composition be assessed -- which may be very difficult to answer under the current circumstances. Is this process going to be an ongoing process, and how are we to respond to these questions in terms of the detail and specificity? Dr. Marks. I think you're muted.

**DR. PETER MARKS:** Sorry about that. Dr. Monto, thank you very much for that question. I probably should have mentioned in my opening remarks that (audio skip) beginning of a conversation about this. And so, I would say that the granularity today can be within a level of comfort that the Committee feels that it can get to.

We would anticipate that before we make any further decision about anything regarding the composition of a booster, and before public health agencies more so than just FDA have a -- make a decision about when another booster campaign might be

recommended, there will at least be another VRBPAC meeting to discuss more specifics or particulars about such a variant selection for another booster. And there will be another opportunity to comment on the timing.

So I would say today's discussion should hopefully be one where people don't feel pressured into making very specific recommendations but rather talk about the considerations that would go into making these decisions, and we'll welcome any thoughts about general timing or general aspects in some cases because we will have other paradigms such as influenza to compare to.

**DR. ARNOLD MONTO:** Thank you, Dr. Marks. Dr. Levy.

**DR. OFER LEVY:** Good morning and thank you, Dr. Marks and Dr. Fink. Very important topics we'll be considering today. In our deliberation, in our framing of this discussion, should we be really focused on the vaccines that are currently approved and authorized, or should we also be taking a bigger picture view?

There's ongoing innovation on the vaccine end. It's possible that additional vaccines might come into play that have different characteristics in terms of durability of protection, breadth of immune response, or different kinds of booster scenarios with different platforms.

So there's some -- already a lot of complexity. But for our conversation should we also consider that angle? That's a tricky one, isn't it, Peter?

**DR. PETER MARKS:** I agree that that could be somewhat tricky. But I think to the extent that it is relevant I think it's -- we would welcome that discussion. If Dr. Fink and I think we're getting very far afield, we'll let you know that (audio skip) within what the Committee thinks might be on the horizon that might be relevant for this coming fall/winter season.

**DR. OFER LEVY:** Okay. Thank you.

**DR. DORAN FINK:** I'll just add that I think, you know, to get the most out of this discussion that will help us in the near term and to keep things in the

realm of what is, you know, practical, what's actionable and achievable, I would place the higher priority on considerations for currently available vaccines because those are the decisions that we'll have to make soonest.

**DR. OFER LEVY:** In the near term. Thanks.

**DR. ARNOLD MONTO:** Thank you. Dr. Hawkins.

**DR. RANDY HAWKINS:** Thank you very much. I just -- although not necessarily related to the current agenda, I just want to draw attention to Dr. Fink's slide about planning ahead and remind us all about the importance of targeted narrative for COVID-19 in human populations. There's a lot of distractions out there. There's a lot of misunderstanding about the vaccine and COVID-19 and really the importance of a targeted narrative on many levels of public health about -- to the public. Thank you.

**DR. ARNOLD MONTO:** And a final question from Dr. Hildreth.

**DR. JAMES HILDRETH:** Thank you, Dr. Monto, and thank you, Dr. Fink and Dr. Marks. You've already made

a decision about boosters recently, to give them to 60 plus and those with underlying conditions. So I'm just wondering why this discussion is being held now when you've already made some major decisions about boosters. So what was the reason for not convening the VRBPAC to make that decision?

**DR. PETER MARKS:** Yeah, Dr. Hildreth. Thanks for that question. I think this question gets asked, and it deserves an answer. So the decision to allow boosters (audio skip) a recommendation right now for older individuals and those over 50 with -- so -- was to basically allow people the option right now, while we still have COVID-19 circulating, to be able to essentially restore protection -- levels of protection based on data that had come from both United Kingdom and Israel indicating some waning of protection.

We consider that as a -- not a major expansion or a major change but something that we looked over the data and felt was reasonable to do at the time. This discussion today is a much larger discussion. It's the discussion of what do we do for the entire population

and what do we do when we think the virus may have evolved further and that may help preclude a major wave in the next season -- fall/winter season. So we feel like this discussion is more around the larger population issue.

We're not saying which population necessarily needs to be boosted come next fall/winter. I think that's for the Committee to discuss -- whether it's the entire population or a segment of the population. And we also, I think, have to think about what goes into that vaccine composition, which are fundamentally, I think, much larger questions than the narrower question of whether a segment of the population could benefit from a fourth dose in terms of protecting against what might be another wave of COVID that could come in the coming months given what we've seen going on both in Europe as well as north of our border in Canada.

**DR. JAMES HILDRETH:** Thank you.

**DR. ARNOLD MONTO:** Thank you both, Dr. Fink and (audio skip). Going on now to our first presentation (audio skip) on -- update on the

epidemiology of SARS-CoV-2 strains. And this will be globalized soon. Dr. Scobie.

**UPDATE ON THE EPIDEMIOLOGY OF SARS-COV-2 STRAINS**

**DR. HEATHER SCOBIE:** Good morning. Can you hear me?

**DR. ARNOLD MONTO:** Yes, we can.

**DR. HEATHER SCOBIE:** Great. So the U.S. has a multifaceted genomic surveillance system for monitoring SARS-CoV-2 variants circulating in the -- in our country. The system includes sequencing data from the national SARS-CoV-2 strain surveillance, CDC-supported contracts with several commercial diagnostic laboratories, and sequences deposited by partners in public repositories such as GISAID and NCBI.

CDC estimates that if a variant is circulating at 0.1 percent frequency there is greater than a 99 percent chance that it will be detected in national genomic surveillance. During Omicron's emergence in the U.S., the sensitivity of genomic surveillance was

1 further enhanced on a temporary basis through rapid
2 screening of PCR specimens with S-gene target failure
3 for confirmation by genomic sequencing and expansion of
4 voluntary airport-based genomic surveillance programs
5 in four U.S. cities.
6 This graph from a recent publication shows the
7 changing landscape of circulating variants by two-week
8 periods during January 2021 to January 2022. Through
9 the first pass of 2021, several variants circulated
10 simultaneously to the Alpha variant in the teal color
11 as this variant was rising to predominance. The Delta
12 variant in orange rose to super dominance and almost
13 completely displaced other circulating lineages in late
14 June 2021, followed by the rapid rise of Omicron in the
15 purple color in December 2021.
16 This fact bar graph shows the national
17 weighted estimates of variant proportions over time in
18 the recent Nowcast projections of circulating
19 SARS-CoV-2 lineages in the U.S. by week of specimen
20 collection by CDC's COVID Data Tracker. The Omicron
21 sublineages depicted in the purple shades have

maintained predominance at 98 percent to 99 percent since late January. The BA-2 sublineage of Omicron, shown in lavender, was 72 percent as of the week ending April 2nd.

I'll note here and show in a minute that despite the rise in the proportion of BA-2 nationally we haven't seen a rise in case incidents to date. This map shows the relative proportions of BA-2 in lavender and other Omicron sub lineages in the darker purple shade across the 10 health and human services regions. You can see that BA-2 is predominant or greater than 50 percent in all regions at this point, and the northeast and west have higher proportions.

The Omicron variant has been shown to have increased transmissibility but decreased severity relative to previous lineages. Omicron has many mutations in the spike genes including 15 mutations in the receptor binding domain as shown in the picture on the right. These mutations are associated with reduction in the efficacy of some monoclonal antibody treatments and a reduction in neutralization by sera

from vaccinated or convalescent individuals.

In 42 lab studies of sera from people who received vaccines approved from the -- in the U.S. an mRNA primary series had 25-fold reduced neutralization of the Omicron variant compared to a reference strain, while people with a booster dose had only a six-fold reduction. In the graph on the right, which shows the relative impacts of variants on neutralization of sera after different primary vaccine series shown in different colors, the effects of Omicron on viral neutralization is greater than previously observed, including compared with the Beta variant which previously had the strongest impact.

I'll also note that reductions in neutralization for Omicron may be underestimated because Omicron neutronization was below the limit of assay detection for many individuals who had received two doses of mRNA vaccines or one dose of Janssen vaccine. And these values had to be imputed or ignored to calculate a fold reduction.

In contrast, neutralization of Omicron was

above the limit of detection in many individuals who either received a booster or vaccinated people who had been previously infected. We note that because of the limits of detection in these types of assays it's difficult to evaluate whether people had the minimal level antibodies thought to be needed to protect against severe disease.

This graph shows the trend in the daily number 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 variant and then the Omicron variant. As of April 5th there have been about 80 million cases of COVID-19 reported in the U.S.

These are the trends in seral prevalence for the estimated percentage of people in the U.S. with anti-nucleocapsid antibodies indicating resolving or past infection with SARS-CoV-2 by age group. These results do not include anti-spike antibodies from vaccination, nor do they reflect the percentage of the population that might have sufficient antibodies to be

protected from reinfection.

The percentages of people with previous infection have increased over the course of the pandemic with noticeable increases observed following the rapid rise of Delta and Omicron variants. Greater seroprevalence was noted in younger age groups, likely related to these groups being eligible for vaccination in later months than the older age groups and potentially related to differences in exposure risks.

This graph shows the trend in the daily number of reported COVID-19 deaths in the United States since the beginning of the pandemic including during the waves associated with the Alpha, Delta, and Omicron variants. As of April 5th, there have been over 979,000 deaths due to COVID-19 repotted in the U.S. These are the weekly trends in COVID-19 associated mortality rates by age group.

The data show that higher mortality is consistently observed in older age groups, most notably on this graph among those aged 75 plus, 65 to 74, and 50 to 64 years of age, as shown in the purple and pink

colors. These are the weekly trends in COVID-19 associated hospitalization rates by age group. Similar to the previous graph you can see higher hospitalization rates in the older age groups with patients aged 65 years and older in red and 50 to 64 years in dark blue having the highest rates.

To date, approximately 218 million people in the U.S. have been fully vaccinated with a primary vaccine series, which is 70 percent of the eligible population age five years and older. And there are about 98 million people who have also received an additional or booster dose, which is 50 percent of the eligible population aged 12 years or older.

This graph shows trends over time and by age group in the percentage of people who have received at least the 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. And we can also see that coverage with the primary series for ages 5 to 11 years, shown with the yellow dotted line on the left, is still relatively

low at 28 percent. Booster dose coverage on the right remains under 50 percent for age groups less than 50 years, as shown in the blue and yellow colors.

Next, we're going to shift to consider case surveillance data from 29 state and local public health jurisdictions, shown on the right. These jurisdictions routinely link surveillance and immunization registry data and collectively represent 67 percent of the total U.S. population with good geographic representation. Reported COVID-19 cases and COVID associated deaths are monitored by vaccination status. It expresses weekly rates and incidence rate ratios among the unvaccinated versus fully vaccinated either overall or with -- or without a booster dose.

This slide shows the age adjusted rates of COVID-19 cases by vaccination status. Unvaccinated people in all age groups have higher case rates than fully vaccinated people in the same age groups. Notably, in February, unvaccinated people aged five years and older had 2.8 times higher risk of testing positive for COVID-19 compared to people vaccinated

with at least the primary series.

This slide shows the age adjusted rates of COVID-19 associated deaths by vaccinations status. Similar to the previous slide, unvaccinated people in all age groups had higher mortality rates than fully vaccinated people in the same age groups, including during periods of Omicron predominance. Notably, in January, unvaccinated people ages five years an older had nine times the risk of dying from COVID-19 compared to people vaccinated with at least the primary series.

Furthermore, people who are fully vaccinated with an additional or booster dose had a noticeably lower risk of testing positive and dying from COVID-19 compared to people who are unvaccinated. This graph also shows the additional benefit associated with being up to date with vaccination including protecting against serious outcomes.

The COVID-19-associated hospitalization surveillance network, or COVID-NET, conducts population-based surveillance for laboratory confirmed COVID-19 associated hospitalizations within a catchment

area of over 250 acute care hospitals, in 99 counties, in 14 states, representing 10 percent of the U.S. population. The standardized case definition is residents in the surveillance area and a positive SARS-CoV-2 test within 14 days prior to or during hospitalization.

Hospitalization rates are -- by vaccination status can be monitored because COVID-NET also relies upon routine linkage to immunization information systems, and these data are a representative sample of hospitalized cases. This graph shows the age adjusted rates of COVID-19 associated hospitalizations by vaccination status. Hospitalizations for COVID-19 were higher among unvaccinated people than fully vaccinated people over time, including after Omicron became predominant in January 2022.

In February, compared to fully vaccinated adults aged 18 years and older, monthly rates of COVID-19 associated hospitalizations were five times higher in unvaccinated adults. This graph shows further disaggregation of hospitalizations among people who are

fully vaccinated with or without a booster dose. In February, compared to fully vaccinated adult's ages 18 years and older with additional booster doses monthly rates of COVID-19 associated hospitalizations were seven times higher in unvaccinated adults.

These COVID-NET data show that hospitalized patients that were fully vaccinated were more likely to have other underlying risk factors, including being older, long-term care facility residents, having a DNR, DNI, or CML code, and having more underlying medical conditions compared with unvaccinated patients.

In summary, in 2021, the U.S. experienced a dynamic landscape of SARS-CoV-2 variants, including Delta- and Omicron-driven resurgences of SARS-CoV-2 transmission. CDC continues to monitor emerging variants like Omicron and BA.2, including their prevalence and impact on disease incidence and severity over time. Monitoring trends in rates of cases, hospitalizations, and deaths by vaccination status has been helpful for monitoring the impact of different variants.

And finally, currently authorized vaccines offer protection against severe disease but it's important to stay up to date with vaccination, including receipt of booster doses in eligible populations. I'd like to thank the following individuals and appreciate your attention. Thanks.

**DR. ARNOLD MONTO:** Thank you, Dr. Scobie. We have a few minutes for questions now. We're a little bit ahead of schedule, and we'll move on after a few questions to the next CDC presentation and then have a more general discussion. So, Dr. Gans.

**DR. HAYLEY ALTMAN-GANS:** Thank you. Thank you for that (audio skip). And since we're here actually to think about a booster specifically, while we all understand that actually increasing the number of individuals (audio skip) in general is a great goal for us all to have, in the data you really didn't talk about the added addition of that booster dose. They sort of seemed lumped together with people who have had two doses as thinking about that as a primary are called fully vaccinated, and then those individuals.

So my first question is breaking down that data so that we can really understand the additional relevance of that dose, which we understand there is data out there. The other piece of it, because we know that immunity in general -- so those -- that is provided by natural disease as well, really considering the epidemiology of reinfections in those individuals, breaking that down for (audio skip). So I guess those are really relevant to the discussion today and I'm (audio skip).

**DR. ARNOLD MONTO:** Dr. Scobie, you're muted.

**MR. MICHAEL KAWCZYNSKI:** Go ahead, Heather. Heather, I think you have your own phone muted. Can you hear me, Heather?

**DR. HEATHER SCOBIE:** I just had to unmute.

**MR. MICHAEL KAWCZYNSKI:** There go you. Now we got it.

**DR. HEATHER SCOBIE:** Okay. Are we able to go back to my slides? I have a few at the end but (audio skip). So I think this helps address your question. I maybe didn't cover it as clearly as I should have. But

this looks by age at the same data I was showing of cases by vaccination status. And the dotted line is those without -- with the primary series only, and the solid blue line is with the primary series and booster dose. And these data go through the end of January.

And so, what we're seeing here, at least in the older age groups, is that there is -- the gap between the people who have the primary series only and the people who have a primary series and booster dose, it is -- there was a clear benefit through -- for quite a while, but the gap has closed a bit in recent months. And it's unclear because of the way these data are analyzed and the limitations associated with surveillance data -- like not being able to control for prior infection, for example, it's unclear whether that's at play, but it likely is.

So, for example, you might expect that a person with a primary series only might have been -- you know, might have had higher rates of contracting Omicron during the recent waves. And so that -- an explanation like that could explain why these people

are starting to look more similar to those who had a primary series and booster dose. And the careful VE studies which are able to control for those factors and which Dr. Link-Gelles will present on next I think will help address that question.

But I did also want to note that in this graph we've recently added the 12 to 17 years old. And you can see that those folks who were vaccinated, you know, kind of in a wave more recently are showing a larger kind of benefit of that booster dose at least right now. And then when you look at death by age and receipt of a booster dose, of course in the younger ages we just have so few deaths, and that's what that is showing. But you can see a clear impact including now amongst older people of that booster dose. So the booster dose is helping prevent death in older ages. And I think that is shown quite clearly in the data.

Does that help address your question? I think there was a second one about previous infection. And unfortunately, there -- that's not something we're able to address with these data at this point. There are

specific states who've tried to address that question because they're able to link to laboratory -- they're able to link the surveillance data with laboratory data and determine who's been previously infected. Notably California and New York have published a nice publication. But the data we currently have at CDC for this -- that I've shown here, we're not able to look at previous infection and move data currently.

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

**DR. CODY MEISSNER:** Thank you, Dr. Monto. And thank you, Dr. Scobie, for a very interesting and clear presentation. My question stems from this issue. We're here to think about when it might be necessary to change the composition of the vaccine. Certainly, one of the parameters that will be important in that consideration will be the rates of hospitalization rates of death due to the strains that are circulating at that particular time, suggesting the vaccine's not as effective as we wish.

So, my question is this. In the state of Massachusetts they keep track of hospitalizations --

COVID-19 associated hospitalizations and break out hospitalizations that are attributable to the infection and hospitalizations that are simply found in a positive -- a positive in a patient who's hospitalized for other reasons. And the data as of April 1st, in Massachusetts, there were 216 COVID-associated hospitalizations and 85, or 39 percent, were because of the infection, and 61 percent were patients hospitalized for other reasons, so more than half.

So I guess the question I have is do you think that number changes with different variants that might have increased infectivity? And can the CDC provide us with that data so that we get a better assessment of hospitalizations that are actually due to a variant that might be circulating. Thank you.

**DR. HEATHER SCOBIE:** Thanks. Yeah, I mean, as you're raising, this issue came up -- the question of with COVID or for COVID came up in a big way during Omicron because, as you rightly pointed out, there has just been -- there was, at that point, just so much higher community transmission. So there were many

people lining up incidentally in the hospital for other causes that had COVID-19 that was detected, you know, upon admission through screening testing.

A lot of the studies attempt to look at whether -- like, I've seen those state data that you're talking about, including some other states, and I do think that there are studies that have attempted to look at, you know, COVID associated hospitalization, not just incidental COVID amongst hospitalized patients. And so, I do think we're able to uncouple that in some cases, and I do think that those studies are ongoing and, in some cases, have been published.

In terms of your question about making the data available, I think we are working hard to make all of the data available as soon as it's ready. So I'm not sure if I've addressed your question but I'm willing to -- if you have any follow-up I'm willing to address them.

**DR. CODY MEISSNER:** No, my -- the only point -- thank you from that answer. My only point is that that will be important data for us to be able to

consider when we're thinking about whether or not there's a need for a change in the vaccine. But -- so I appreciate your answer.

**DR. ARNOLD MONTO:** Thank you. Doctor --

**[BREAK]**

**MR. MICHAEL KAWCZYNSKI:** All right. Welcome back again. That was just a little bit of an unscheduled break, but we're going to pick up right where we sort of left off with our next presenter. And I'm going to hand it back to Dr. Arnold Monto. Dr. Monto, are you ready?

**DR. ARNOLD MONTO:** Next, we're going to hear again from CDC, Dr. Ruth Link-Gelles, who will be (audio skip) five minutes.

**COVID-19 VACCINE EFFECTIVENESS IN CHILDREN AND ADULTS**

**DR. RUTH LINK-GELLES:** Hi, good morning, can you hear me?

**MR. MICHAEL KAWCZYNSKI:** Yes, we can.

**DR. ARNOLD MONTO:** Yes, we can.

**DR. RUTH LINK-GELLES:** Great. So, this presentation is broken up into three sections, by increasing severity of the outcome under study, including infection, emergency department and urgent care visits, and hospitalization, including critical illness and then, within each outcome section, by age group. Since there are multiple age groups and outcomes and a lot of data to track, every slide with have an indication, shown here in blue, of the endpoint and population displayed. So look for that in the upper left-hand corner of each slide.

I'll begin by discussing vaccine effectiveness data for infection, mostly in the U.S. Throughout the presentation, I focus on U.S. data, although there is one exception at the end of the section on infection. So I'll start with talking about the CDC platform known as PROTECT, the Pediatric Research Observing Trends and Exposures in COVID-19 Timelines. This is a prospective cohort study in children aged 4 months to 17 years that

includes weekly swabbing, regardless of symptom status, and uses a person-time model with adjustment for propensity to be vaccinated, site, and SARS-CoV-2 circulation.

Results were separated by age group, 5 to 11 years and 12 to 17 years. Here we see the results published in CDCs MMWR showing VE for Omicron variant among 5 to 11 year olds on the top, 31 percent, and for Delta and Omicron among to 12 to 15 year olds on the bottom, with an estimate of 59 percent for that age group in the 14 to 149 days since vaccination during the Omicron period. Note the very wide confidence intervals for the longer time since vaccination among the 12 to 15 year olds, which makes it difficult to interpret waning here. Moving on now to the increasing community access to testing, or ICATT platform, which is national community-based drive-through testing data from pharmacies.

This platform uses a test negative design, where cases are persons with at least one COVID-like symptom and a positive NAAT test, and controls are

symptomatic with a negative NAAT test. This is previously published adult data for the Delta, in orange, and Omicron, in blue, periods by time since second dose, shown on the X-axis, with VE on the Y-axis and the dotted lines showing the 95 percent confidence intervals. You can see the lower starting VE for Omicron compared to Delta and much quicker waning, including zero in the confidence interval by three months after the second dose in adults.

And now, we show the same adult data for Delta and Omicron and overlay data from adolescents, 12 to 15 years of age, in black, and children 5 to 11 years of age, in pink. Note here the much shorter follow-up time for the 5 to 11 year olds due to vaccines being recommended for them in November. Generally we see almost identical patterns across the age groups, with two doses of mRNA vaccines providing roughly 60 percent protection initially and quickly waning to about 20 percent and lower by a few months after the second dose.

Now moving on to the J&J vaccine during

Omicron only. Here we have different Janssen booster schedules on the left, two doses of Janssen, one dose of Janssen, followed by one dose of mRNA vaccine or three doses of mRNA vaccine as a comparison. Time since last dose, zero to one month or two to three months is shown as well. And you can see that generally the two Janssen doses produced the lowest VE, although there was little evidence of waning, even against infection where we usually see the most waning. The other two schedules produce similar VEs, and though there was statistically significant waning for both schedules, they both remain significantly higher than the Janssen only schedule.

Finally, I just want to share this slide from the UK showing VE for BA.1 and BA.2. Though BA.2 has not been prominent in the U.S. long enough to estimate VE here, the UK has had higher rates of BA.2 for a while and looked at VE by sub-lineage for Pfizer, Moderna, and Astra-Zeneca primary series with a Pfizer or Moderna booster dose. You can see here that VE was generally comparable after both two and three doses of

vaccine. So, to summarize the VE for infection during Omicron, mRNA vaccines tended to start at a lower VE for Omicron than Delta and wane faster. Patterns of waning by time since second dose looked similar across age groups. Waning was different for those who received two doses of Janssen and lower overall versus schedules that included an mRNA vaccine. And, finally, from the UK we have data showing that VE for BA.1 and BA.2 are similar.

I'm now moving on to vaccine effectiveness for emergency department and urgent care visits. The VISION network is a multi-state network based on electronic health care 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. This is VE from the VISION network for 5 to 11 and 12 to 15 year olds during the Omicron predominance. Like ICATT, we have similar VEs for two doses of mRNA vaccines for the two age groups.

For adolescents 12 to 15 years of age who had longer time since vaccination, we see waning for the

period greater than 67 days since the second dose. This is the adult two dose data during Delta, in blue, and Omicron, in magenta, with time since second dose shown on the left-hand side. You can see the clear waning by time since second dose for both variants, with lower overall VE for Omicron compared to Delta. Moving now to three dose VE for adults. Here again Delta is in blue and Omicron in magenta. On the top half of the slide we have time since third dose for all adults and on the bottom for immunocompetent adults only during Omicron.

We can see that while VE is lower for Omicron, and some waning is evident, it's perhaps less extensive in the immunocompetent group compared to all adults, which includes immunocompromised individuals, a pattern we'll see again in the hospitalization VE estimates. And now, moving on to hospitalization, starting with children. The Overcoming COVID Network is a test-negative VE platform specifically aimed at children and adults hospitalized at 31 pediatric medical centers in 23 states.

As with other platforms, cases have CLI and a positive test, while controls have CLI and a negative test. Here we have VE of two doses against hospitalization for children 5 to 11 years of age during Omicron and adolescents 12 to 18 years of age during Delta and Omicron. We can see the same pattern as for less severe outcomes with lower VE during Omicron compared to Delta. However, unlike for less severe outcomes, we do not see evidence here of waning against hospitalization, shown here out to 44 weeks in the adolescent group, even during the Omicron period.

Overcoming COVID was also able to look at VE separated by hospitalization without life support and hospitalization with life support or death. And you can see in the bottom half of the slide, during Omicron, VE of two doses for critical disease was significantly higher than for non-critical disease. Overcoming COVID also looked at the effectiveness of vaccination during pregnancy at prevention of infant hospitalization. This is mostly pre-Omicron/Delta, but you can see the high VE of 80 percent afforded by

receipt of a second mRNA dose during the second half of pregnancy. Additional work to extend this analysis to Omicron is underway.

And then, finally, also from the Overcoming COVID Network, they looked at VE against multi-system inflammatory syndrome in children. On the left you can see different critical care endpoints. 95 percent of MIS-C patients were unvaccinated, and zero fully vaccinated children required any critical care. On the right you can see VE calculated using different controls to look at biases that may be associated with different MIS-C definition. No matter the control choice, two doses of Pfizer are 89 to 92 percent effective at preventing MIS-C.

Now, revisiting the VISION Network, this time looking at hospitalization, this slide shows VE for all variants for 5 to 11 year olds on the top and 12 to 15 year olds on the bottom. For the 5 to 11 group, you can see there were only two breakthrough hospitalizations during the study period, which included two months after children in that age group

were fully vaccinated. While the point estimate for 5 to 11 year olds, 74 percent, is lower than the point estimate for 12 to 15 year olds, 92 percent, that's likely due to the younger age group, which included 67 percent Omicron cases, for which VE is lower compared to earlier variants while the older age group included only 15 percent Omicron cases.

Now looking at VISION hospitalization data for adults with Delta in blue and Omicron in magenta. Like for the emergency department and urgent care visits, two-dose VE for Omicron is significantly lower than for Delta. But we see that the third dose provides substantial improvement over two doses. And, as with the ED/UC data, those furthest out from the third dose during this period, shown here in the red box, were vaccinated before the booster recommendation was in place, meaning many of them were likely immunocompromised individuals receiving a third primary series dose versus healthy individuals receiving a booster dose.

To resolve this issue, here the VISION Network

restricted their waning analysis during Omicron to immunocompetent adults only. On the left you can see three age brackets, as well as time since the third dose. For both immunocompetent adults 18 to 44 years, and immunocompetent adults over 65 years, there's no evidence of waning of VE against hospitalization during Omicron. In the middle age bracket, 45 to 64 years, there may be a hint of waning, although the confidence interval for the four to six month period is wide, making interpretation somewhat difficult.

Finally, VISION also looked at the Janssen vaccine, and showed the same pattern we saw previously for VE against infection. A single dose, or two doses of Janssen, was generally lower, although a booster dose of Janssen or an mRNA vaccine was significantly better than no booster at all. VE of three mRNA doses was significantly higher than Janssen plus any booster. Finally, the IVY network covers hospitalized adults at 21 medical centers in 18 states and uses a test-negative design with cases having CLI and a positive test and controls being SARS-CoV-2 negative.

IVY also looked at three-dose VE among immunocompetent adults and, similar to VISION, found no evidence of waning 120 days plus after the third dose for adults of all age groups on the top and adults 65 plus on the bottom. IVY also looked at VE for critical illness or in-hospital death in two recent publications. Here they found that VE of two doses for critical illness or death during Omicron was 79 percent, and VE for three doses was statistically significantly higher, at 94 percent.

So, now moving on to summarize, this slide shows all the data for children and adolescents. Outcome is listed on the far left, with increasing severity as you go down the slide. In general, we see a pattern of increasing two-dose VE with increasing severity, although obviously wide confidence intervals for worse outcomes. And now, for adults, we have two-dose VE in green and three-dose VE in magenta, again, with increasing severity as you go down the slide and increasing VE with increasing severity, just like in children. The patterns here show the clear benefit of

a third dose over a second dose during Omicron and the highest VE, 94 percent, for three doses for critical illness and death out to a median of 60 days follow-up.

So, in summary, we saw similar patterns for VE across age groups during Omicron, with limited protection, especially for two doses, against infection but strong protection of two doses, and even stronger protection of three doses against the most severe outcomes, including hospitalization, MIS-C, and critical illness and death. While it was too early to assess three dose protection for adolescents, and children 5 to 11 years of age are not yet recommended for a booster, we are likely to see similar patterns for younger age groups for the third dose. I want to acknowledge the individuals shown here on this slide, and I'm happy to take any questions. Thank you.

**DR. ARNOLD MONTO:** Thank you so much for a very clear presentation. I really liked your summary slide, which brings it all together. Questions from our group. Let's see. Let's look at our list. We have hands raised by Dr. Levy.

**DR. OFER LEVY:** Thank you for that presentation. Very helpful. A (audio skip) when we compare outcomes such as infection (audio skip) what extent are we able to correct behavioral differences (audio skip) in terms of wearing masks or social distance (audio skip) have they been applied to these analyses?

**DR. RUTH LINK-GELLES:** Sure. So (audio skip) individual (audio skip) one that is difficult to do in any (audio skip) the (audio skip) one that I showed for (audio skip) a little bit of the bi-(audio skip) that platform (audio skip) those things might effect vaccination (audio skip) and the VISION Network (audio skip) hospitalization platform (audio skip) analysis score includes a number of things (audio skip) than things that (audio skip) change by behavior (audio skip) control for, I wouldn't say it's (audio skip) bias could remain there.

**DR. ARNOLD MONTO:** Dr. Marasco.

**DR. WAYNE MARASCO:** Can you hear me?

**DR. ARNOLD MONTO:** Yes.

**DR. WAYNE MARASCO:** Hi. So, when we measure vaccine effectiveness, you're really not -- the denominator there of knowing what the difference in levels of immunity are between those that become infected and those that do not really needs to be, I think, fleshed out a bit more because you have vaccine responsiveness, but you don't have the correlate that we really want to be able to know to look at vaccine effectiveness at the decision to, one, to reboost, for example.

So, I guess my question is we know that we're going to get waning immunity. It sort of becomes more steep at four to six months. That's the timeframe that we're looking at. And is it all people in the population that require it, or we learn from this waning response what it takes to remain protected?

**DR. RUTH LINK-GELLES:** Sure. So I think -- so these studies are not designed to look at correlates of protection or antibody response or anything like that. We're looking purely here at a sort of real world definition of infection or hospitalization or an urgent

care visit. I will say we did look -- and the VISION data -- I'm not sure if we can put my slides back up, but we did look -- in the VISION Network, they did a first analysis that included immuno (audio skip).

I'm not sure if I -- it doesn't look like I have actual control over the -- oh, there we go. This is the VISION analysis, and so if you look here, this includes all adults. So it would include immunocompromised as well as immunocompetent adults. And you can see the apparent waning in that four plus month period I think that you were referring to. The thing here that I would caveat is that, based on the timing of when this analysis was done and when boosters were recommended for the general population, this is going to pick up mostly vaccinated individuals who were vaccinated before we had a booster recommendation for the general population in place.

So, these would have been a lot of immunocompromised individuals that were receiving a third dose as part of a primary series as opposed to healthy individuals getting a booster dose. And so,

when they went back and looked at that -- and they looked here just at immunocompetent individuals, so individuals that we don't expect to have particular conditions that would result in higher rates of vaccine breakthrough -- they really didn't see any signal for waning in two of the age groups and maybe a hint in one of the age groups. And so, I think by doing these analyses of the real world data, we're able to parse out a little bit some of the different risk factors for vaccine failure. But you're absolutely correct here. We're not looking at correlates of protection.

**DR. WAYNE MARASCO:** Thank you.

**DR. ARNOLD MONTO:** Thank you, and, Dr. Link-Gelles, isn't it true that some of the studies are trying to collect blood spots and things like that to help elucidate the question about correlates?

**DR. RUTH LINK-GELLES:** Yes, absolutely. We do have a number of cohort studies that are much smaller that do collect blood for antibody testing and looking at correlates of protection. I didn't show any of that data here. Most of our vaccine effectiveness platforms

are quite a bit bigger because of the power required to look at real world vaccine effectiveness. For example, the VISION Network has an extremely large catchment area in the millions, and so they are not collecting specimens. They're relying on electronic health care records. But we do have separate data coming in from cohort studies that's attempting to look at the correlates of protection.

**DR. ARNOLD MONTO:** Thank you. We're going to move on now to a sequential presentation from, first, Dr. Sharon Alroy-Preis from Ministry of Health from Israel and a presentation from Dr. Ron Milo from the Weisman Institute in Rehovot. First, I believe, Dr. Alroy-Preis.

## ISRAELI EXPERIENCE WITH FOURTH BOOSTER DOSES IN OLDER ADULTS

**DR. SHARON ALROY-PREIS:** Thank you. I hope you hear me well. We're actually doing this presentation together. It has been a joint venture by

the Ministry of Health and four academic institutions in Israel. You see their logos above in this slide, and it's been a pleasure to work with them and to look at the data from different perspectives, validating one another. I would like to say that both myself and Ron, all the groups that we're representing have no competing financial interests to disclose. Israel Ministry of Health and Pfizer have a data sharing agreement. However, in relation to all booster effectiveness studies presented here that was done by the four institutions, only the final results of the analysis were shared. So it was not done with Pfizer.

So, based on the rapid rise in Omicron cases in the world that we saw in different countries, South Africa and then England and then other places and the early evidence of waning of the third dose protection for confirmed infection in Israel, we decided to begin fourth dose vaccination campaign on January 2nd. I have to say that it was a combination of things, really anticipating a surge of cases, knowing that our at-risk population, the elderly population, of adults four

months old booster, that is waning off for confirmed infection.

Knowing from previously that the second booster was waning off for confirmed infection, and then we saw severe disease and mortality -- and so we decided to be proactive and offer a fourth dose for all those who were 60 and above and medical staff that received the third dose at least four months ago. What we got is a compliance of about 50 percent in the 60 plus population. Out of nearly 1.2 million individuals that were eligible, we had roughly 600,000 patients -- people getting the vaccines. I'm moving this to Ron to explain the analysis of the vaccine effectiveness, and then I'll continue with the safety data that we have.

**DR. RON MILO:** Hello, everyone. So I hope you can hear me okay. Our study analyzes data of about 1.2 million people eligible for fourth dose. Out of those 1.2 million people, about half -- about 0.6 million, received the fourth dose. Another 0.6 million received a third dose and were eligible but chose not to receive the fourth dose. During the analysis period, which was

between January 10th and the beginning of March, there were, unfortunately, a strong wave of infections in Israel, leading to about 160,000 confirmed infections and 1,700 severe hospitalizations by the NIH definition. And, therefore, we have quite a lot of statistics you can see here in order to analyze the results.

Let me show you the main results that we have. Let me know if there's any problems in hearing me or seeing the results. In this slide, and starting from the X-axis, this is the time since the fourth dose in weeks, and on the Y-axis, you can see the protection as a function of the time since the fourth dose, looking at the rate ratio, which means those with three doses and those with four doses. As you can appreciate, this is rising such that at week four, you can see two different analysis in terms of outcome.

In blue, the results for confirmed infection and in red, you can see the result of severe illness. In both cases, we adjust for as many confounders as possible to see the quadrant for some regression. It's

the same analogy that we also analyze in previous studies published in *The New England Journal of Medicine*, and this specific study has been published yesterday by the *New England*. And we're adjusting there for age, for gender, for sector, or for calendar day, et cetera.

If you look at the blue dots, you can see that it say it's week four, the two-fold creep in the rate of infection for those with a fourth dose versus those with a (audio skip) dose and (inaudible) waning significantly by week eight.

In contrast, when you look at severe illness -- - and severe illness, just to reiterate, is based on the NIH definition, which you can see at the bottom right of the resting respiratory rate other than 30 breaths per minute. You can see the results about oxygen saturation, et cetera. You can see that the rate is about three- to four-fold lower pending a very significant three-quarters decrease in the rate but then, consistently around that value, week four, week five, and week six.

We did not have data at that point. It was submitted for peer review, for extra weeks. When we have and we update this -- and I'll show you in a few slides the more updated results with some extra weeks. This was in terms of the factors of full reduction in the rate. We also looked at the adjusted rate difference, which is also entered, and you can see them summarized in this table. It shows some related wave of infections.

We had some significant difference both in the three doses and, again, the internal control group, or internal control group, like we just mentioned briefly, is what you see here in terms of what happened on days three to seven, which is a point in which the same people have decided -- it's the group that decided to take a fourth dose. But that was a time when they still very minor in terms of confirmed infection, and, therefore, we use them in terms of control group. But, for both of them, we see the risk and full reductions in rates and a significant change in the rate difference.

Here, you can see an update with a few more weeks, following week six, in terms of protection from severe illness. I show you before up to week six, and here you can also see week seven, week eight, and week nine. You can see the overall rate was in the range of somewhere between two-fold and four-fold, meaning somewhere between the margin of vaccine effectiveness of 50 percent and 75 percent beyond the protection supplied by the third dose.

Finally, I want to present to you the results of the protection against mortality in the age group, for eligible ages 60 and above, again, with the same methodology. And you can see that within that age group, it has a margin of vaccine effectiveness of 76 percent versus the third dose, which is 4.2-fold decrease. Again, the internal control group, we see a 55 percent margin of vaccine effectiveness, which is about 2.2-fold.

The second group is somewhat lower for the internal control group may very well arise also in the vaccinee effect, meaning people that got all the way to

having a severe disease may actually decide not to take the vaccine. Overall, we see somewhere between two-fold and four-fold further protection against mortality, beyond what was given by the (audio skip) dose. Also, see at the bottom, the absolute rate difference is per 100,000 risk days versus these different groups. And now, we'll move on to discuss the safety.

**DR. SHARON ALROY-PREIS:** Thanks, Ron. So, this is the data -- the safety data. It is on all those who received a fourth dose, so it's not just for 60 and above. As you can see, we had more than 750,000 people receiving the fourth (inaudible), it's the purple bar.

The indication was, as we said, 60 years and older, individuals 18 years and older with comorbidities and risk factors for developing severe COVID-19 and also their caretakers, facility residents and their caretakers, 18 and above, caretakers of the elderly, obviously healthcare workers, and other workers with significant occupational exposure who

wanted to get a fourth dose.

I should mention that the rate of adverse events here are per million doses, and we are capturing adverse events that happen within 30 days of the vaccine. It's updated until the end of March. And limitation is most of the data that you'll see here is based on passive surveillance. The only exception is myocarditis, which we are still doing active surveillance on, which means we are calling all the hospitals asking them to report all cases of myocarditis, related to the vaccine or not, to make sure that we have a link that can be contributed to the vaccine. So all the things that are under passive surveillance could be subject to underreporting.

Here is the adverse events reported for the fourth dose. We had 442 mild reports, 12 serious reports, and you can see the definition of serious reports -- the international definition of serious reports by the FDA. I should mention that all hospitalization and death reports following vaccinations are examined by an independent clinical

work group that gets all the clinical data to establish a connection to the vaccine.

So, this is the data in more detail. You see that most of the reports we had are on more systemic reaction, fever, feeling sick. That was the most part. We had 12 serious adverse events that I will go into detail in a minute and three other adverse events that you see details at the bottom. One was atrial fibrillation three days following the vaccination for a person with cardiac disease; another case of suspected myocarditis that did not require hospitalization and was referred to MRI; a case of elevated LFTs that was found on routine screening -- did not require hospitalization.

As you can see on the table on the right, those are fourth dose vaccinees who were vaccinated with Pfizer vaccine. So here is the detail on the serious adverse events that we got. We had four cases of pericarditis. You can see them detailed. Some of those cases have risk factors for pericarditis. We had a case of renal failure exacerbation for a patient with

chronic renal failure in days after the vaccine. We had a case of mortality in a very complex individual with dementia and multiple comorbidities, COPD, diabetes, one day after the vaccine. We had a case of pneumonia, CVA, a case of myocarditis that, as you can see, had at admission evidence of active COVID-19 infection. So we are not sure exactly whether to contribute the myocarditis to the vaccine or to the infection that can cause myocarditis as well.

We had a case of a myocardial infarction in an individual 60 to 64 years of age with no relevant medical history, a case of acute kidney failure 21 days after the vaccination, and a case of seizure in a patient with a medical history of epilepsy. And here is the summary of the myocarditis cases of all the vaccines that were given. If you want to focus in on the purple bars, this the fourth dose. We had two cases. One of them was a case that did not require hospitalization. And the other one, as I mentioned, is a case that in addition to receiving the vaccine, also had evidence of active COVID-19 infection upon

admission to the hospital. So this is, in general, the data on the safety. And we will be happy to answer any questions that you have, either on vaccine effectiveness or our safety data.

**MR. MICHAEL KAWCZYNSKI:** Arnold, are you ready?

**DR. ARNOLD MONTO:** Thank you. Right. Thank you, as usual, for (audio skip).

**DR. SHARON ALROY-PREIS:** (Audio skip) previously (audio skip).

**[BREAK]**

**MR. MICHAEL KAWCZYNSKI:** All right. Welcome back to the 172nd Vaccines and Related Biological Products Advisory Committee Meeting. Again, I think we got everything all worked out now, so we shouldn't hopefully have any more unscheduled breaks. And, with that, we're going to reconvene, and I'm going to hand it back to Dr. Monto. Dr. Monto, are you ready?

**DR. ARNOLD MONTO:** Right. Welcome back.

We're now going to go into a session which is going to be looking at the future of SARS-CoV-2 variants from various standpoints, modeling, and other devices and mechanisms. First, we're going to hear a two-person presentation. First is the reverse of the program, we're going to hear first from Trevor Bedford from the Hutch in Seattle, Washington. And then, from John Beigel, from the NIAID, NIH. So, please, Dr. Bedford.

**PREDICTING FUTURE SARS-CoV-2 VARIANTS: SARS-CoV-2 EVOLUTION UNDER POPULATION IMMUNE PRESSURE**

**DR. TREVOR BEDFORD:** Thank you, Dr. Monto. I'm not seeing my slides up right now, are you seeing my slides?

**DR. ARNOLD MONTO:** I am.

**DR. TREVOR BEDFORD:** Michael, could you -- oh, there we go. Okay. The slides are now up.

**MR. MICHAEL KAWCZYNSKI:** Yep. Give me one second, I will give you your rights real quick here. We just want to make sure we have everything all set up

there. One moment. Oh, I see what I -- you should have it now and take it away.

**DR. TREVOR BEDFORD:** Yes, I do now. Thank you. Okay. Thank you all for the introduction to speak. I'm going to be talking about continuing SARS-CoV-2 evolution. Briefly I want to disclose grant support from the National Institutes of Health, and the Howard Hughes Medical Institute to work in methods for evolutionary forecasting.

As I think we're all aware, the pandemic in 2021 has been -- and forward has been characterized by the repeated emergence of variants of concern viruses. Here is just an example, Alpha and Gamma, where basically what we've seen is a new kind of raft of mutations all appearing on the same kind of genetic background. That virus then rapidly spreads either just locally or globally, displacing existing diversity. And so we've seen this again and again. These viruses tend to have been -- most of this evolution has been in S1 domain. So, if we characterize the amount of adaptive evolution across

the genome, we really see a focus in S1 in particular. This is expected, both due to host adaptation as well as immunoscape.

So, if you look today at the different genetic diversity that we've seen over the course of the last two years, there's been a lot of genetic diversity that's merged. We have the previous variants, Alpha, Beta, Gamma, et cetera, Delta over here. Omicron is actually these two fairly distinct sublineages of the BA.1 and BA.2. At a genomic level, they're quite distinct, as distinct as say, Beta and Gamma. But if you look at the RBD spike, that is quite similar. So it suggests you can suspect similar immune responses to BA.1 and BA.2. What we've seen then is that over the course of the pandemic, as these variants have emerged, the more successful ones have rapidly swept through the population and displaced existing diversity.

So we had a diversity of variants existing in Spring 2021 that then Delta emerges and then sweeps to basically fixation. So, by October/November 2021, Delta's over 99 percent of all SARS-CoV-2 viruses. And

it had emerged in late Fall 2020, and so this time period of just one year to basically reach fixation is remarkably fast. The faster influenza, H3N2, takes generally three to five years for a new strain to emerge and sweep to fixation. And then, in this case, Omicron was even quicker, where an emergence in early October 2021 then gets to very high frequency in the population in just the course of about four months -- three or four months.

And now we're seeing BA.2 emerge and start to increase in the BA.1 background. It appears to have some intrinsic transmission advantage relative to BA.1, even if immunity is actually quite similar. And so, again, this is very rapid population dynamics relative to, say, influenza H3N2. We can see that if we look back at spike protein, we can kind of maybe understand what's going on here -- where there's these three phases of the pandemic so far where these kind of early, quote, non-variant viruses don't have very many mutations. And spike S1 we get this first tranche of variants, Alpha, Beta, Gamma, Delta, with 8 to 10

mutations and this recent phase with Omicron, with 25-30 mutations in S1 and kind of a large divergence here.

Then, if we then just look at S1 through time, and again try to kind of quantify what's going on, we can see over the course of 2021 there's been about 12 substitutions per year in spike S1. This is ignoring Omicron at the moment and just looking over the course of 2021. And we can compare that to influenza, again. So, here, I'm converting this into per amino acid residue because, like S1, it's about twice the length of the equivalent domain in influenza of HA1, but then we see that SARS-CoV-2 so far has been evolving about twice as fast as influenza H3N2, about four times as fast as influenza H1N1, and about ten times as fast as B-Victoria.

And this means that if we look here at Omicron-like viruses, in just two years' time, since the start of the pandemic, we have accomplished about five years of equivalent evolutionary H3N2. So from both an accumulation of mutations in S1 and from a population dynamic standpoint, the evolution has been

remarkably fast so far. We can maybe expect it to slow down as things stabilize a bit, but this to me suggests a fairly adaptable and evolvable protein that is likely to keep on evolving in response to selective pressure.

So, with Omicron, as we've seen -- this is just an example -- where the amount of vaccine effectiveness drops substantially, especially with two doses, we have a lot of immunoscape to vaccine-derived immunity as well as infection-derived immunity. And this caused these very large epidemics throughout the world where we can see -- this is cases in blue of Delta, red of Omicron, on a log scale here. And so we can see that the Omicron epidemic comes in as exponential growth, where we can see that as the straight line on a log scale, across all of these different geographies. This two to three day doubling -- this very rapid exponential growth results in very large epidemics in terms of caseloads that then start to decline once there has been enough population infected and Omicron-specific immunity in the population because of these large epidemics.

So, to get a sense of scale for this, if we look in the U.S. we see that we estimate that 9.8 percent of the population has confirmed cases of Omicron through March 1st, with a large majority accumulating after December 15th. We don't know this number exactly for the U.S. We have it for the UK, but the best guess for the U.S. is that we have a current case detection rate of about one in five infections. So this is almost 50 percent of the U.S. infected with Omicron in the span of just 10 weeks, which is, again, a remarkable number.

Comparing this to flu, seasonable influenza infects perhaps 10 to 20 percent of the population in the span of 20-ish weeks. So, again, a large attack rate due to this very rapid evolution. Going forward, what we can expect is I think that we can be pretty confident that there will be additional kind of flu-like, in quotations, drift within BA.1 and BA.2. So we can expect an amino acid change of three appearing that slightly escape from existing immunity.

Those viruses will do better and will spread

locally and perhaps regionally and perhaps globally. And that will get population turnover, like we do with influenza, and further evolution within BA.1 and BA.2. However, we can also -- perhaps given that we've seen Omicron-like emergence events once, we can expect that it could occur again. So, that Delta -- we could have, for example, an emergence of an Omicron-like variant from a Delta background that would then be wildly divergent. And exactly assessing the probabilities here is quite difficult, so basically all I think we have to go on is that we've had one observation of a large, kind of wildly divergent Omicron-like emergency event in 2.35 years of virus evolution.

And so this is compatible with a wide range that we could have the true underlying rate of Omicron-like emergence events every year -- about 1.5 years, or it's compatible with, say, once every decade. And we really don't know whether these wildly divergent viruses will be a common feature or a rare feature of endemic SARS-CoV-2 evolution. But playing this uncertainty forward, we get this sort of distribution

where in the next 12 months we suspect that the more likely scenario is not an Omicron-like emergence event but perhaps a less likely scenario of Omicron-like emergence.

So then, thinking forward of scenarios, again we have a more likely scenario, which I think we should be planning for, of evolution within Omicron BA.2 and BA.1 to further increase intrinsic transmission and escape from Omicron-derived immunity and, then, a less likely scenario, where we have another wildly divergent variant emerge that drives a large epidemic, the way that we have just seen with Omicron.

But in general, from everything we've seen, again, it appears that S1 domain and SARS-CoV-2 is a very adaptable beta protein, and we could expect a lot of evolution going forward. And we should have methods to keep up with this evolution in terms of vaccination platforms. And with that, I will stop and hand it over to John.

**PREDICTING FUTURE SARS-CoV-2 VARIANTS: SARS-COV-2 ANTIGENIC SPACE**

**DR. JOHN BEIGEL:** All right. Thank you to Dr. Fink and the FDA for inviting me and Dr. Monto for inviting me to speak. So, before I start, for my disclosures, as part of my federal official work at NIAID I was involved with the Moderna Phase I study -- so with the mix and match study that included Pfizer, Moderna, Janssen, and Novavax, and then also with a new study called COVAIL that I'll talk about today that also includes industry partners such as Moderna.

So, given the uncertainties that Dr. Bedford described, taking the next point to be challenging. And I think until we know more, we have to understand how to react to the new strains. So what I want to do in the next few minutes is just talk about how we're viewing the antigenic space, how we are thinking about tackling the knowns around Omicron but also other antigenic areas. Work by NIAID collaborators and a group called SAVE and others used neutralization assays

coupled with what's called antigenic cartography to describe the antibody response.

And it's important that these maps are just visualization tools. All it does is take neutralization data, but it helps visualize antigenic space. It's helps to visualize risk. And it really helps us understand how to address this problem. The antigenic cartography and antigenic landscapes are common tools for influenza. Just -- many VRBPAC members know this, but just to make sure we're all on the same page, I just want to spend a minute describing what this visualization tool is. For antigenic cartography, you basically take a cohort. You do neutralization titers to multiple strains. So in this scenario they did the mRNA 1273. They looked at neutralization titers. Then you determine a distance from the highest titer, and you determine that dilutions. And that equates to a distance, and you plot that distance on a map.

And you let the computer -- and you do this for every single sample, and you let the computer go

through. And it starts to triangulate where the antigens and where the sera line up. And then you take additional groups and, in this case, convalescent serum and, again, you do the titers to multiple strains. And you put it on an antigenic map, and you repeat that as needed to address all the questions. And you start developing this very complex map where all these strains and sera are triangulated, and you start seeing the relative distance between these. The map only reflects relative distance and relative dilutions. But you can also add to that landscape, and that landscape shows titers across the variants to inform titers, but also starts informing areas of vulnerability.

That landscapes are -- you can plot individual landscapes, and you can plot that over time. Landscapes are consolidated to a GMT to understand -- a geometric mean, to understand the cohorts. And you can start looking at different cohorts as needed. The work by Derek Smith -- and that's most of the data I've shown so far -- they've been able to look at these landscapes to these different cohorts. And you start

seeing the -- in the upper left, the mRNA 1273 sera looks very different, and it kind of tapers as you get towards Omicron. But then, if you look at the 351 sera, it's a very different profile. And then you look at the 617.2 sera, and again, it's a very different profile, really high towards Delta, really low back towards Beta. Again, you start visualizing where the cross-neutralization titers might exist.

So, if we target Omicron, it assumes Omicron recurrent or drift from Omicron. And that might be the most likely, but there's also other antigenic spaces that we worry about. And the scenario here, in the upper right, is there might be a new antigen that -- a new virus and a new antigen that maps towards Beta. So that's significantly far from Omicron, almost as far as back to prototype, but it's really close to things we've seen before, Beta. And the same scenario at the bottom, where it's Delta. So significantly far from Omicron, significantly far from prototype. And there's the possibility that the emerging viruses are going to be in this area.

So the question is how do we use the variant vaccines to target these different antigenic spaces?

So to try to address this we've developed a study called the COVAIL Study for the COVID Variant Antibody Immunologic Landscape Trial. And it's a population -- and it's a population of people that received a primary and a booster. It can be homologous, heterologous. It's age greater than 18. They're stratified by age. It's any infection status, those that are infected or not, but stratified by infection. And they are randomized to one of six arms. And those six arms are in the top right and reflect five different strategies of different vaccine candidates, either prototype or variant or a mixture of the variants. And then there's also arm three, which is a slightly different question, which is a two-dose. So does it take one-dose or two-dose to try to antigenically convert somebody and form that landscape in a direction that we want.

This study just began enrolling last week. We've got -- we're planning 24 sites, and early

responses for a given variant and vaccine might increase across the landscape. And we've seen that in other studies where you see a general increase. And, again, it might drift in one direction, but a general increase across the landscape. But then the later time points we anticipate would show a differential response. And, again, I just sort of came up with these hypothetical landscapes. But you can see that they might be quite different, so in the event that there's a new variant, or maybe when there's a new variant, we can test that sera. And you can really say that that vaccine that was used in the bottom left, that hypothetical vaccine three, is really targeting more towards Delta and not towards this new variant and is not the strategy what we want.

But then you can start seeing how we can use this data with the different vaccines and start understanding how to modify that landscape and target certain antigenic areas. So, just to wrap it up, we think there is likely to be continued evolution for the SARS-CoV-2 virus. As Dr. Bedford pointed out, it could

be evolution within Omicron. It could be another Omicron-like emergent event any place in that map. Ideally we learn to pick vaccine strains based on anticipated evolution, but we're not there yet. Until then we need to understand how to use available vaccines, the prototype to variant and alone or in combinations to modify antibody responses and target the different antigenic spaces. Thanks.

**DR. ARNOLD MONTO:** Thank you, both. Thank you, John. Thank you, Trevor. We're going to have just a few minutes to try to catch up for these two speakers. We may be able to have a more general discussion after the next two presentations because they're all related to the same issues. Hands raised, if I can recognize them. Mike, unless I'm missing it, I don’t see any hands raised.

**MR. MICHAEL KAWCZYNSKI:** All right. Dr. Rubin is first.

**DR. PRABHAKARA ATREYA:** Yes.

**DR. ARNOLD MONTO:** Okay. It's not showing.

**DR. PRABHAKARA ATREYA:** Yeah, it is in the

middle, Dr. Rubin, Dr. Offit, and Hayley Gans in that order.

**DR. ERIC RUBIN:** Thanks Mike and Prabha. Those were very interesting presentations. Thank you both. I guess the question is we don't really have a great, very specific level of antibody that correlates highly with protection. Dr. Beigel, when you have those very complex figures, it's hard to know where on that surface that you're drawing protection is occurring. That does make it very difficult to interpret these results. We know what kind of an antibody response can be generated. We just don't know if it works.

**DR. JOHN BEIGEL:** I think it's a reasonable criticism, if you will. I didn't highlight it, but there was a great plane across the middle that represented an IV50 (phonetic) and we could really set that anywhere. You're right. We don't have -- I mean, we do know there's some correlates for neutralization titers. It's not perfect, but we do know the risk starts going up as those titers get lower. So we can

set that plane to 50. We can set that to 100 and start understanding as those landscapes are drifting in that area and as the emergent viruses in that area. That's probably not the strategy that we would want.

**DR. ARNOLD MONTO:** Okay, Dr. Offit.

**DR. JOHN BEIGEL:** For some reason, I can't hear you.

**DR. ARNOLD MONTO:** -- with the hands raised.

**DR. PAUL OFFIT:** Thank you. Thank you Trevor and John for that presentation. My question, I guess, is in line with Dr. Rubin's question, which is have you looked or are you interested in looking at T cells, specifically T-helper cells, cytotoxic T cells?

Because really, if we're talking about protection against serious illness, which is the goal of this vaccine, that may be the better correlate. And you'd like to know to what extent these viruses are drifting in terms of those what have been today conserved epitopes that are being recognized by T-helper cells or cytotoxic T cells. I think it's been an unappreciated part of the immune response in terms

of study.

**DR. JOHN BEIGEL:** Yeah, it's a critical point, and I didn't go through all the details for the sake of time. But we are selecting TBMCs and anticipate to do a lot of T cell work and B cell work just to the points you've raised.

**DR. PAUL OFFIT:** Thank you.

**DR. ARNOLD MONTO:** Dr. Marasco, did you have your hand raised, or is it from before?

**DR. WAYNE MARASCO:** Can you hear me? So, Trevor and John, thank you. My question really is to John's experimental design. John, do you expect to be, with that approach, to broadening the sort of memory cell response from the earlier strain to be able to capture the latter strain? Or is this more one of being able to elicit new memory cells into the immune memory response?

**DR. JOHN BEIGEL:** Yeah. The short answer is I don't know which one we will get. The ideal response is exactly what you said that you'd run it and you actually flatten that landscape and that you're not

longer sort of drifting down towards Omicron. But you can actually flatten it, and you can cover more. Now, whether that's a realistic expectation, I don't know. And that's why we do the study. And, also, whether it takes one dose or two doses to do that, I don't know. And that's why we built in a two-dose arm. So, I hope that we would be able to broaden the landscape, but I don't think we know enough about how to immunogenically shift people's immune response yet.

**DR. ARNOLD MONTO:** Thank you, doctor. Dr. Gans. Final question before we move on.

**MR. MICHAEL KAWCZYNSKI:** Dr. Gans, do you have your phone muted?

**DR. PRABHAKARA ATREYA:** Dr. Gans, we can't hear you.

**DR. ARNOLD MONTO:** We can't even see you. Okay. We're going to have to move on because of the press of time. Next we're going to have a, again, a two-person presentation "Modeling of Future U.S. COVID Outbreaks." Dr. Murray and Dr. Mokdad will be talking, one after the other, and then we'll have the questions

afterwards. Dr. Murray.

**MODELING OF FUTURE U.S. COVID-19 OUTBREAKS**

**MR. MICHAEL KAWCZYNSKI:** Dr. Murray?

**DR. CHRISTOPHER MURRAY:** Yes. I'm not sure I understand your format here. Am I supposed to share the slides, or is somebody at your --

**MR. MICHAEL KAWCZYNSKI:** Nope, they're already up there. If you want to go ahead, and you should see two little arrows below the slide deck.

**DR. CHRISTOPHER MURRAY:** It says nothing being shared at my end. Here, maybe they're coming up.

**MR. MICHAEL KAWCZYNSKI:** Oh, hold on. And go ahead and turn your camera on as well, sir.

**DR. CHRISTOPHER MURRAY:** All right. I unfortunately don’t see anything on your platform.

**MR. MICHAEL KAWCZYNSKI:** That's okay. You should see two little arrows at the bottom of the PowerPoint, sir.

**DR. CHRISTOPHER MURRAY:** Yeah, I don’t even

see the PowerPoint at all. Maybe it's coming. There's just a circle going around and around.

**MR. MICHAEL KAWCZYNSKI:** Go ahead and start. I'll move your slides for you, sir.

**DR. CHRISTOPHER MURRAY:** All right. Let me see if I can find my slides. This presentation is about how we model at IHME the pandemic in the U.S. and elsewhere. The slides say, if you can see them -- if you advance, I'm going to cover first -- how the sort of first step in how we think about this, and that is how we understand past the sort of basic model structure. If you go to model slide three, the main insight that we have to have is to capture waning immunity. And so, if you're looking at slide three --

**MR. MICHAEL KAWCZYNSKI:** Sir, you actually stopped sharing the slides. I have to reload them.

**DR. CHRISTOPHER MURRAY:** I never --

**MR. MICHAEL KAWCZYNSKI:** That's okay. That's okay. That's okay. I will reload your slides here, because you -- it's quite all right. And, again, what's the name of your slide deck, sir?

**DR. CHRISTOPHER MURRAY:** I think it is "IHME COVID Forecast April 6."

**MR. MICHAEL KAWCZYNSKI:** IHME, is that what you said?

**DR. CHRISTOPHER MURRAY:** Yes.

**MR. MICHAEL KAWCZYNSKI:** Bear with me. There we go. Here it comes. Just, sir, at the bottom of the slide deck, when it comes loading in, you will see two little arrows when it comes up. Just going to take a moment now.

**DR. CHRISTOPHER MURRAY:** Is it showing at your end?

**MR. MICHAEL KAWCZYNSKI:** Yes, it's right here, sir. I'll put it back in for you.

**DR. CHRISTOPHER MURRAY:** Okay.

**MR. MICHAEL KAWCZYNSKI:** Do you see it now?

**DR. CHRISTOPHER MURRAY:** There we go. I can see it now.

**MR. MICHAEL KAWCZYNSKI:** There we go.

**DR. CHRISTOPHER MURRAY:** Thank you. All right. So this shows the model structure that we use

to capture the waning of immunity and to model both vaccination boosters, as well as the competition between variants within the transmission dynamics model. Moving on, next slide. We have been using sort of meta-analysis of all the available studies, the waning of immunity, both for severe disease, hospitalization, and death, as well as for preventing infection.

Those are -- as everyone on this call knows, they're quite different. This is the waning from the available data on preventing infection and likewise for severe disease. So those go into our modeling framework. Critical to understanding Omicron and where we see future directions is this understanding of the immunoscape. And so, we have a matrix in the modeling between the different variants, and then we have a distribution from a similar meta-analysis of the waning of natural immunity or infection-acquired immunity.

So that's the sort of very high order background. Now, the most important part of making sense of where we are is the analysis of past infection

because our analysis, or anybody's analysis, is going to make sense of transmission looking back. And the way we do that is we triangulate using cases, hospitalizations, and deaths, using seroprevalence data to directly measure the infection detection rate. Trevor Bedford, for example, mentioned the 20 percent figure. We try to estimate this empirically from state-specific and country-specific comparisons of seroprevalence data.

The seroprevalence data also has to be corrected for the waning of sensitivity of antibody, depending on the specific antibody test. And so that's also part of this analysis. And then we ought to differentiate antibody positivity that's related to vaccination from not. This all comes together in this example here for Colorado. Green, on the top row, is cases and then the infection detection rate in the middle panel, and then the top right is infections that we estimate. And then the middle row is the same analysis based on hospitalization, and then the bottom row is the analysis based on deaths. And so we try to

triangulate on these to come up with past infection.

That tells us about, however you want to think about it in terms of a transmission's dynamics model, what is effective R or in our framework, the Beta T coefficient that is multiplied by the number of infection sources at any given moment in time. Similar analysis for Illinois. Bottom line here is that these -- at least in the U.S., when you do this sort of triangulation, it all fits together rather well. Some country's that is not the case. But for the U.S. the triangulation on the different sources gives us a very coherent view of past transmission.

And you can see how much more dramatic the Omicron wave has been in terms of infection, up on the top right there, than previous waves of different variants. Now another thing that goes into our assessment, which matters for some states in the U.S., matters a lot for other countries, is to correct for under registration of death. The way we do that is we analyze excess mortality. I won't go into the method. This was published *The Lancet* a few weeks ago. But

basically we are trying to validate the assessment of COVID using registered deaths by week and, in some cases, like Russia, by month.

When you do that, you get these excess death rates, and I only put up this map that's from the paper to point out that within the U.S. excess death rates have very tremendously sort of North/South gradient, with intriguingly the lowest excess death rates in the U.S. being North Dakota and the highest in the sort of states on the southern border. Now, this is the crude excess death rate, and because the infection fatality rate is so strongly related to age more than any other cause of death that we know about, it's interesting to look at the next slide, which is the standardized mortality ratio.

So this is observed excess mortality divided by expected based on your age structure. And when you look at that, then suddenly COVID starts to look more like most other diseases. Once you correct for age, the excess death rate starts to look highest in low and middle income countries. But compared to other high

income countries, some of the southern parts of the U.S. have fared poorly. And then amongst the middle and to high income countries, Eastern Europe and Russia have done extremely poorly. So this all goes into our analysis of the past and into how we model out the future trajectory.

So, for modeling Omicron, as Trevor mentioned, very rapid invasion. And this is documented now in multiple, multiple locations. And so we know, in terms of modeling Omicron, that the transmission as well as the immunoscape are quite high. We also have to build in the reductions in vaccine effectiveness for both infection and severe disease as a function of each of the vaccines. Now, not every cell in this matrix is known, so we have to approximate the full matrix of all the different vaccines in the world against the different variants for infection and severe disease using an algorithm that uses which of these cells we actually have direct observations for and then, essentially, sort of estimation by analogy for some of the missing vaccines.

I won't belabor the Omicron attributes. Trevor covered them, but fortunately for us all, given how transmissible Omicron is, the fact is it's quite a bit less severe than Delta has been a blessing. And, of course, it's critical to the future forecast if we think the next variants are from the Omicron lineage, or we're going to see a reversion back to higher severity disease. Okay. So where do we get what's forecasts? We're at the tail end of the global Omicron wave, with the exception of China.

We suspect that we'd be modeling that there would be takeoff of the Omicron wave in China, sort of every week next week. That has not happened because of the successful pursuit of the Chinese lockdown and triple testing strategy that got rid of Omicron in Beijing in February. And we'll see if they're successful in Shanghai or not. But we do think that China will pursue this aggressive zero COVID strategy at least until October. And so probably we won't see the massive Omicron wave that will eventually come until later in the year for China.

The BA.2 wave that has spread through some, but not all, countries in Europe seems to last about three weeks. So if it does come to the U.S. probably a short shoulder or rise. Our model suggests it will not have much impact. And the reason we see this differentiation in different countries of Europe and also likely in the U.S. has to do, we believe, with how much past infection with other variants and then how many people have been infected with Omicron already.

And more than 60 percent of the world has been infected with Omicron already, and in the U.S. that number is about 50 percent, at least in our models. So here's the forecast. These are the short-range forecasts out four months. We do run our models later in the year, and first let me talk to you about four months. The infections here we do not see, as you can see on this graph, a much, if any, of the BA.2 bump. There will be a small bump in reported cases. You can barely make it out on the right-hand side for reported cases. And then we expect numbers without a new variant, or just evolution of Omicron -- we see in our

long-range models a winter return.

And so we get the -- what Trevor was describing, that seasonable pattern, due to waning immunity and seasonality. And that shows up in the longer range models. The way we've been trying to handle the evolution of new variants, which I won't show, is made up scenarios. What if a new variant does emerge in May or June or July with different attributes? And perhaps not surprisingly, when we do that you can get large outbreaks, depending on the variant, and considerable mortality if you revert back to a severe variant. The key factor that we have yet to build into the models that we are working on is the availability of antivirals, particularly Paxillin, because that will change not the course of the transmission but changes our estimates of death shown on the next slide.

So here's our predicted mortality. Again, we're seeing dropping to very low levels in the summer. It starts to come back next winter. And then, when we run these sort of random scenarios around variant

evolution, you can see a return of mortality. But even a Delta-like severity with Omicron level of transmission, or more than Omicron, if antiviral access is heavily scaled up, we get a much smaller mortality peak than we saw, for example, with Delta last year or the winter peak last year.

So that's sort of the main findings. Here's the summary around the BA.2 shoulder. It's very interesting when you dig into the details in Europe of which countries have had these BA.2 shoulders versus not, and as seen in the previous graphs, we don't currently forecast much of a BA.2 wave. But it's certainly a very real possibility given what we've seen in some countries in Europe, but our models don't want to have a BA.2 wave.

Now, one way to look at this is our, estimated from within the model, susceptibility to Delta and Omicron, where we are peaking at about 80 percent right now protection against Omicron and likely slightly lower numbers for BA.2 but not much. And then you go into this period of slow but steady decline because of

waning immunity. And so that's how we will see, as we go later into the year, the return of transmission based on these modeled estimates of susceptibility. Last on the slides here is nothing that Trevor has not already covered. But we do, in our various hypothetical scenarios, see the critical factor that alters the trajectory of death is access and availability of antivirals. That really makes a very big difference.

And then, this endogenous response, even though we don't expect governments to impose much in the way of mandates politically going forward, to the extent that we've seen in the last two years, considerable behavioral adaptation by those at risk by wearing masks and social distancing -- when you add that in you will get some dampening of transmission if there is a major new variant, even without the implementation of mandates. If you do have mandates return, then of course you get more dampening. Those are other sort of factors that will influence the trajectory quite considerably. And then I think, if

both Ali and I will -- I've made the presentation for both of us, and Ali and I can answer questions as needed. Thank you.

**MR. MICHAEL KAWCZYNSKI:** All right. Arnold, you there?

**DR. ARNOLD MONTO:** I am. I can -- right? Here I am.

**MR. MICHAEL KAWCZYNSKI:** There you go.

**DR. ARNOLD MONTO:** Thank you for compressing the two presentations into one. We're open for questions. If I can find where the hands are raised in this -- okay. I found it. Dr. Bernstein. I think you're muted. At least, we don't hear you.

**DR. HENRY BERNSTEIN:** Can you hear me now? Sorry.

**DR. ARNOLD MONTO:** Yes.

**DR. HENRY BERNSTEIN:** Yes? Sorry.

**DR. ARNOLD MONTO:** Yes.

**DR. HENRY BERNSTEIN:** The presentation's very intriguing. My question relates to slide number 20. You talked about 80 percent use of masks, and I was

wondering what impact you anticipate in broadening mitigation factors along that path?

**DR. CHRISTOPHER MURRAY:** So, in previous variants, the scaled up use of masks had a really profound effect. What we have seen in the models is that transmissibility of Omicron is so high the prevalence in the community is so high that the marginal effect at the community level of mask use has been relatively small. That is not necessarily the case for future variants, but right now, essentially everybody who was susceptible, at least in the way we model things, ends up getting infected over some period of time.

Now, in reality, there's probably -- we've seen pockets of people -- well, we've seen this phenomenon -- like, look at New Zealand -- where you finally get in a vaccinated but unexposed population -- you get widespread community transmission, and then you get a very long, sustained peak. And the only way to account for that is that you're not reaching a peak where all susceptible's are being infected and coming

down. You are progressively reaching different groups of people that are susceptible, which does suggest that even with Omicron that there is some effect of sort of social distancing, as groups emerge from being very cautious. But at least the way we model the sort of 50 percent reduction at the individual level of transmission, it doesn't have a large scale population impact for Omicron.

**DR. HENRY BERNSTEIN:** Thank you.

**DR. ARNOLD MONTO:** Thank you. Dr. Meissner, the last question for this group of presentations.

**DR. CODY MEISSNER:** Thank you, Dr. Monto. Thank you for the series of interesting presentations. My question relates to why we're seeing so many variants. Based on the fact that SARS-CoV-2 has a proofreading function in the polymerase complex, that is not found so frequently in other RNA viruses. Why do we see mutations that are in SARS-CoV-2 that are greater than what we see in influenza, in view of the fact that there is this activity?

And then, secondly, one of my biggest concerns

has been that there would be a mutation in the receptor binding domain that would enable the virus to attach to non-ACE2 receptors because the other coronavirus -- not all coronavirus -- the seasonal coronaviruses don't all -- and even, I think MERS, doesn't bind to ACE2. So, if that happens, that's really a problem because our current vaccines won't work. And this thing will surge once again. Do you have any comments about that, please?

**DR. CHRISTOPHER MURRAY:** That sounds like a question more for Trevor Bedford on the evolutionary front than for us. But Ali or Trevor?

**DR. ARNOLD MONTO:** Trevor, are you still on?

**DR. TREVOR BEDFORD:** I'm sorry, I had missed the question. Can you repeat it?

**DR. CODY MEISSNER:** Yes. In view of the existence of the proofreading frame that's part of the polymerase complex of SARS-CoV-2, why are we seeing more mutations than we are with other viruses? Because I think you said it several times what we see with influenza, which I don't believe has that activity.

And then, secondly, is there a risk of a new mutant with a capacity to bind to non-ACE2 receptors and thereby escaping the immunity induced by the current vaccines?

**DR. TREVOR BEDFORD:** Yeah. Thank you. So, for the first question, yeah, that's definitely a theme in 2020 for thinking about the rate of evolution that we see with SARS-CoV-2. The per nucleotide mutation rate of coronaviruses is low, lower than, say, influenza. But much more of the rate of evolution is dictated by the adaptability, the evolvability, robustness of the kind of protein at question. And so it appears that spike one -- S1 of spike protein is quite adaptable, and so that seems to be much more what's driving the rate of evolution.

And we see this across influenza HAs as well for what appears to dictate the rate of evolution between H3N2, H1N1, and the B viruses. In terms of the second part of the question, I don't -- there is shifts at an evolutionary timescale of receptor binding, but in terms of what we'd expect for SARS-CoV-2, I think

that we can be pretty confident that will stick with ACE2, at least for a decent amount of time.

**DR. CODY MEISSNER:** Thank you.

**DR. ARNOLD MONTO:** Thank you. And now, switching gears, it's my pleasure to introduce Dr. Kanta Subbarao, who is now the head of the collaborating center -- WHO collaborating center in Melbourne, Australia, where it is the middle of the night. Thank you, Kanta. She is formerly at NIH and at CDC. So very familiar with what we do in the U.S. Kanta.

## WHO PERSPECTIVE ON VARIANTS FOR COVID-19 VACCINE COMPOSITION TECHNICAL ADVISORY GROUP ON COVID-19 VACCINE COMPOSITION (TAG-CO-VAC)

**DR. KANTA SUBBARAO:** Thank you very much. Arnold, can you give me a thumbs-up if you can hear me?

**DR. ARNOLD MONTO:** I can hear you.

**DR. KANTA SUBBARAO:** Perfect. Great. So, thank you very much, and as Arnold said, it is the

middle of the night. It's 2:25 in the morning. But I am here to talk to you a little bit about what the WHO is doing and thinking about the impact of the emergence of variants on the SARS-CoV-2 vaccines.

The WHO put together a new advisory group, and so TAG stands for Technical Advisory Group. That was called together to make recommendations to the WHO on the methods to assess the impact of variants of concern on vaccines; to provide an interpretation of available evidence on the effect of variants of concern on vaccines, including, but not limited to, vaccine effectiveness; and to recommend to the WHO for each COVID vaccine platform adaptations, if any needed, so that the vaccines continue to provide net protection against variants of concern.

The background is very familiar to all of you. I've heard parts of today's presentations but not all of them. But certainly we all know that the evolution of SARS-CoV-2 could substantially impact the COVID-19 pandemic, as it has done, and may require adaptations of the currently available countermeasures.

Adjustments of the vaccine composition may be needed to optimize the performance of the COVID-19 vaccines because of the emergence of variants of concern. And the regular production and review of available evidence is critical to assess the impact of the variants of concern on countermeasures to issue timely recommendations on potential modifications and to identify need for further research and investigation.

The WHO periodically organizes consultations with independent groups of experts. And so this TAG-CO-VAC, which is the Technical Advisory Group on COVID-19 Vaccine Composition, has been put together to review the evidence and analyze the implications of emerging variants of concern on the performance of COVID-19 vaccines. So the TAG-CO-VAC may recommend to the WHO adaptations of vaccine composition from a global public health perspective and guided by principles of equitable access.

There's a lot of information sharing and cross-reporting among WHO expert committees. A few of them are listed here. The Expert Committee On

Biological Standardization, ECBS, provides recommendations and guidelines for the manufacture, licensing, and control of blood products and related in vitro diagnostic tests, biotechnology products, and vaccines, along with the establishment of WHO biological reference materials.

The Strategic Advisory Group of Experts on Immunization, SAGE, is charged with advising the WHO on overall global policy and strategies ranging from vaccines and technology, research and development, to delivery of immunization and its linkages with other health interventions. The Strategic and Technical Advisory Group for Infectious Hazards, called STAG-IH, provides independent advice and analysis to WHO Health Emergencies Program on infectious hazards that may cause a potential threat to global health security.

And there's the TAG-VE, that has been meeting regularly since 2020, but got the new name of TAG-VE, that periodically monitors and evaluates the evolution of SARS-CoV-2 and assesses if specific mutations and combinations of mutations alter the behavior of the

virus. If you look at the COVID-19 Advisory Group landscape at the WHO, it's a multidisciplinary mechanism of external experts. And the aim is to monitor and assess SARS-CoV-2 variants and to evaluate their impact on countermeasures, including vaccines, but also therapeutics, diagnostics, and effectiveness of public health and social measures.

So from the virus standpoint, the monitoring and surveillance falls to the TAG-VE, which I just mentioned. On the vaccine side, there's collection of research, evidence, and assessment that's been done for the entire duration of the pandemic by the R&D Blueprint for Epidemics. Many of you would have been on their calls and webinars -- and the TAG-CO-VAC, which is this new committee that I mentioned and then, on the policy side, the vaccine implementation and policy side with SAGE.

The TAG-CO-VAC is comprised of 18 members. I'm sure you can't read all of the fine print, but there is a link up there. And I'm chairing this committee for the first year, and David Wentworth from

the CDC is the vice-chair of the committee. We have members from all over the world with a very broad range of expertise. They're virologists. They're epidemiologists. They're people with vaccine expertise and vaccine implementation expertise. And we're supported by a secretariat at the WHO.

We have formed two subgroups to make some of the presentations to the full committee. There's a subgroup that's looking at developing the framework that will describe the decision-making process of TAG and the data that we will require. And we have a strain selection subcommittee that is specifically looking at the immunogenicity and cross protection data to inform any proposed updates to vaccine composition. This is how we plan to approach this. There will be proposals made by these subgroups to the full membership of TAG-CO-VAC for review and endorsement. And the WHO facilitates direct exchanges between TAG-CO-VAC and other WHO advisory groups, the regulatory authorities, and COVID-19 vaccine manufacturers.

We're very cognizant of the fact that we're in

this effort together and that each -- that the vaccine manufacturer, the regulatory authority, both play very important roles. And the role of this committee is primarily to address strain composition. So we've made two interim statements over the last -- since the beginning of the year. The first was posted on the 11th of January, and the key messages are that the current vaccines protect well against severe disease and death. And that is (audio skip) protection against severe disease and death is more likely to be preserved than protection against infection, or symptomatic infection with the current vaccines for the COVID Omicron variant.

And we really need to urge and accelerate broader access to primary vaccination, particularly for groups at greater risk of severe disease because the current vaccines do provide good protection against severe illness and death. But we do need to encourage the development of COVID-19 vaccines that will have an impact on prevention of infection and transmission, in addition to protecting against severe illness and

death.

And until such vaccines are available, and as the virus continues to evolve, the composition of the current COVID-19 vaccines may need to be updated to ensure that there is -- that we achieve protection. So the options that we listed to consider would be a monovalent vaccine that elicits an immune response against the predominant circulating variant. But this option faces the challenge of the rapid emergence of SARS-CoV-2 variants and the time needed to develop or modify the new vaccine. And certainly I heard the previous talk about the predictions of when and where the next variant might emerge from.

The next option would be a multivalent vaccine containing antigens from different SARS-CoV-2 variants of concern. And, of course, ultimately a pan SARS-CoV-2 vaccine, a pan-sarbecovirus vaccine would be a more sustainable, long-term option that would, we would hope, effectively be variant-proof.

We also put out one more statement at the beginning of March where we highlighted the substantial

uncertainties around the evolution of SARS-CoV-2 and the challenges in updating these vaccines with the paucity of data on variant-specific vaccines. We continue to review available data to optimize vaccine mediated protection against prevalent circulating variants of concern. But we really still strongly support the urgent and broad access to current vaccines for primary series and booster doses, especially for groups at risk of developing severe disease.

And we continue to encourage COVID-19 vaccine manufacturers that are developing variant-specific vaccines to share their data on the performance of these vaccines. We're interested in the magnitude and the breadth and the longevity of the immune responses generated by the variant-specific vaccines. I think that is my last slide, so I will turn it back to Arnold and see if you have any questions.

**DR. ARNOLD MONTO:** Kanta, since you have been involved in influenza strain selection for a number of years, could you tell us the process, in a few words, which is impossible -- but I know you can try -- about

how influenza strains are selected as a template for the process that might be going on here in the future?

**DR. KANTA SUBBARAO:** Yes. So, when we talked about how to approach this in the TAG-CO-VAC, essentially we can use as a model the one vaccine that is updated regularly, and that's influenza. Or we could do what we do for influenza and tailor it specifically to SARS-CoV-2. So there's some nuances that will be different from what we can do with influenza, and we can talk about those. But what we do for influenza is that we have a wealth of information on genetic sequence data.

We also have a lot of information about antigenic characteristics. So we typically have data on about 3- to 5,000 viruses that are characterized antigenically to see how they relate to reference viruses which will include viruses that were circulating in the previous year, as well as representative viruses from the different genetic clades that are circulating. We're looking to see if there's antigenic change because, after all, the

vaccines work by inducing immunity, and so the genetic sequence data alone is not sufficient. We really need to see how much antigenic relatedness there is.

We take that information, and our colleagues at Cambridge University generate antigenic cartography maps so that, as you've seen in one of the previous presentations -- so it's a way to visualize the antigen change. In addition to those, we have epidemiologic data. So, essentially, if we have a new variant that is antigenically distinct, and we see it occurring in more than one area, typically more than one continent, causing significant disease, that would be a trigger for consideration. And then last but not least -- and so, the antigenic characterization is done using ferret antisera. But we take advantage of the fact that when we inoculate ferrets intranasally with an influenza virus, they make a very monospecific or strain-specific response, so we can take advantage of ferret antisera to characterize antigenic differences.

And I will get to what we can do, how this would all play into COVID-19. So, in addition to these

data, we also collaborate with two groups of modelers, who help us predict, and Trevor, who gave one of the previous talks, is one of the people that participates in these discussions and provides us their advice on where they think -- the prediction of which clade will dominate. So all of this information is taken together to -- and we also, very importantly, have to have a virus that can be shared around the world with vaccine manufacturers to generate a vaccine.

When we move this kind of discussion to COVID-19, to SARS-CoV-2, there are a couple of notable differences at this time. We have much less antigenic characterization data than we do genetic sequence data. We need that genotype to phenotype link, and like heard in the previous presentation and certainly know from around the world that there is an attempt to do that. We need to make sure that we get very broad coverage of surveillance around the world, which is done by the Global Influenza Surveillance and Response System For Influenza.

So we need to be sure because we don't know in

fact whether we will have region-specific differences or regional differences or global decisions. The third thing that we know for influenza is that at least in the temperate climates it's a winter disease. And so we can actually make a vaccine strain selection decision even in advance of the next year's epidemic. We don't know what the seasonality of SARS-CoV-2 would be yet. So it's difficult to sit here and say that there is a certain timeline in which we can make these decisions. So there are a lot of moving parts, but I think we will use what we know about influenza as the basis to try to put together some of the information that we need.

**DR. ARNOLD MONTO:** Just to monopolize for a minute more, how does this relate to the actual manufacturing of the vaccine in terms of having to produce four components, typically, rather than just one, and the timeline?

**DR. KANTA SUBBARAO:** Right. That's an interesting question. I mean, I should have said also that with influenza we currently have three -- at least

three vaccine platforms -- three or four vaccine platforms. We've got inactivated vaccines that are made in embryonated eggs. We have inactivated vaccines made in cells, recombinant vaccines, and life attenuated vaccines. With COVID-19 vaccines we've got quite a few more platforms. And, in some cases, it's just a single gene, and in other cases it's the whole virus.

So, with influenza, each of the four components in a quadrivalent vaccine, or three components in a trivalent vaccine, are manufactured independently and then mixed together. We don't know what -- and this will be a matter for manufacturers and regulators to figure out what the implications are for a COVID-19 vaccine if it needs to have more than one component because, of course, anytime a multivalent product is made, we have to be sure that each of the components are as immunogenic as they would have been alone.

**DR. ARNOLD MONTO:** And the manufacturing, in theory, waits until the recommendations are made.

**DR. KANTA SUBBARAO:** True. With influenza --

**DR. ARNOLD MONTO:** In theory.

**DR. KANTA SUBBARAO:** -- the manufacturers previously would be (inaudible) systems, we keep in close touch. They have regular discussions with them and bring them up to date on all of our deliberations. And there is a date after the strain selection meeting where all of the manufacturers are informed at the same time about what the recommendation is. Now, having said that, the recommendation is in fact just a recommendation, and each country's national authority makes a decision as to what their vaccine for their country should be.

But the manufacturers are notified at the same time. So our hope with TAG-CO-VAC is to work with manufacturers and keep them updated on our discussions, as we do for influenza. But the manufacturers making COVID-19 vaccines are not all familiar with the influenza vaccine process. So there's a lot of sort of discussions going on to make sure that it's transparent and clear and a partnership.

**DR. ARNOLD MONTO:** Okay. Thank you for my protracted questioning. But Dr. Wharton.

**DR. MELINDA WHARTON:** Thank you. That was really interesting, and I'm delighted to know that under WHO's leadership this is going on. We're all trying to think forward under these conditions of just massive uncertainty. And, yet, in temperate climates I think we are anticipating we may be dealing with a winter wave and want to anticipate it appropriately and maybe prepare for it. Is it your expectation that the Technical Advisory Group will be making some kind of recommendation this summer related to potentially a strain change or a bivalent vaccine or some other changes in current vaccine strategy, or is it too early to say?

**DR. KANTA SUBBARAO:** Yeah, so I can't give you a timeline, but we are certainly discussing the issues around the Omicron and BA.1 and BA.2 very actively. I must say that when the committee was formed, we were talking about Delta and then suddenly had to drop that discussion and move on. And then we were discussing

BA.1, and now there's BA.2. So it is very hard to have enough data, as all of you know, the concern with -- you could say we need a vaccine against the prevalent virus, but we do know that the Wuhan-based vaccines have performed very well.

And it's only the Omicron strain that is really an antigenic variant compared to the Alpha was antigenically very close to Wuhan, and Delta showed some full reduction in neutralization. But it's not anywhere near what Omicron is. And that we could see on the antigenic cartography. So Omicron is really in a place by itself.

And what we know from influenza is that if we go down into a very strain-specific vaccine, that there is a risk that if a variant emerges from the original part of the phylogenetic tree, we might be further away from the breadth of protection that we're getting from the Wuhan-based vaccines. So we're in the midst of those deliberations, and all I can say is stay tuned. We'd love more data, so anyone who has data we'd welcome it.

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

**DR. ADAM BERGER:** Hi, hopefully you can hear me at this point. Thank you so much for the presentation. It was really helpful to hear what the WHO is thinking. I've been thinking of what (inaudible) today is to consider factors and data that should be used to determine whether and when not to (audio skip).

Based on the data that was presented earlier by both CDC and Israel though, it appears that vaccine efficacy against hospitalization and critical illness remains high, between 78 and 88 percent, if I'm remembering my numbers correctly, across all age groups, even though confirmed infection protection wanes over the same time period.

Since these factors are somewhat going in divergent directions, I wonder if you might talk about WHO's thinking about the use of infection itself in making a positive case determination. You noted specifically that until -- I'm trying to remember to remember the words that were up on the screen. Until

vaccines can be developed that prevent infection that the composition may need to be updated. So I assume that WHO has made a determination that infection rates really should be playing a factor here. Would you mind just commenting on the thought process behind that?

**DR. KANTA SUBBARAO:** Yeah, so I'm afraid that I didn't -- I probably missed a few of the words in your question. But let me rephrase what I think I heard, and you can give me a nod if I've got it right. But I thought you were asking what the WHO's thinking is about prevention of -- the use of vaccines to prevent infection. Is that correct?

**DR. ADAM BERGER:** Correct.

**DR. KANTA SUBBARAO:** Yeah. Speaking for -- you know, essentially paraphrasing what our committee has been discussing is the sense that although the vaccines that we currently have provide some protection against infection -- and they certainly did with the original Wuhan strain and the Alpha variant -- they are not providing robust protection against infection with Omicron and that we recognize the need for next

generation vaccines in which that protection is improved.

But the current vaccines that we have today are quite effective in preventing severe illness and death. And so we are saying that we should recognize the role that our currently available vaccines can play in primary immunization around the world and booster immunization as well.

**DR. PAUL BERGER:** Right. I guess the question I have on that is so in that case where you're having divergence, where you've got -- the infection rates aren't necessarily being controlled, in fact, the immunogenicity is waning. The severe effects of COVID are being managed well by the current vaccines, so should infection be a factor that dictates whether or not to change current vaccine composition is really what I'm trying to get at. And I thought from what you were saying that WHO has made a positive determination that infection rate itself should be a factor in making a change to the composition. So is that correct, or did I get that a little bit off?

**DR. KANTA SUBBARAO:** No, I think that is what we said in the interim statement. How much that single factor will weigh compared to antigenic change and the other possibilities of what happens in a prime and unprimed population and what sort of breadth we would get with the new vaccine component compared to what we have with the current, all of those are factors that go into the discussion. So the infection alone is not the full factor, but it is a factor that we would consider. We would all like to see less infection and less transmission.

**DR. PAUL BERGER:** I think we are in definite agreement with that. Thank you.

**DR. ARNOLD MONTO:** Thank you. Thank you, we're going to have to move on. I'm going to make a proposal, Dr. Marks and Dr. Fink, that we next hear from Dr. Johnson, and then we will have the open public hearing, which is fixed in time, and then listen to Dr. Weir's comments at 2:30. Does that sound reasonable?

**DR. PETER MARKS:** Dr. Monto, that certainly sounds reasonable to me, and I think it'll make things

flow very reasonably.

**DR. DORAN FINK:** Yes.

**DR. ARNOLD MONTO:** Okay. Thank you. So now we will hear from Dr. Robert Johnson at BARDA, who will be speaking to us on perspectives of varying vaccine development and production. Dr. Johnson.

## COVID-19 VACCINE STRAIN SELECTION - POINTS TO CONSIDER FOR MANUFACTURING TIMELINES

**DR. ROBERT JOHNSON:** Good afternoon. Thanks so much. As Dr. Monto indicated my name is Robert Johnson, and I am the director of medical countermeasures program at the Biomedical Advanced Research and Development Authority, or BARDA, within the Office of the Assistant Secretary for Preparedness and Response, or ASPR. I should mention my standard conflicts of interest. I have no financial conflict of interest.

However, during the past two years, as a Department of Health and Human Services federal

employee and as part of my federal official duties and work at BARDA, I have been involved in all aspects of managing COVID-19 vaccine development procurement and distribution. So, as I mentioned, BARDA sits within ASPR, who is designated as the Health and Human Services lead for coordination of the COVID-19 response. Over the last two years, BARDA has partnered with manufacturers and funded the large scale manufacturing, development, and/or procurement of six COVID-19 vaccines, including the three vaccines that currently are available in the United States under emergency use authorization.

Based on this experience, as well as the experience according to seasonal epidemic influenza vaccine development, we were asked to address the question of when does the strain selection need to be made in order to ensure product availability in the fall. Unfortunately, there is no one specific date or day, nor is it actually a single decision that has to be made. Rather the date will be specific to each manufacturer and the timing of several regulatory

decisions that will need to be made.

And that's what I'd like to discuss over the next 15 minutes. You've heard, actually -- just as a Q&A from the last discussion, you heard a lot of the assessment that there's similarities between what we do with influenza vaccine in terms of strain collection every year and how it could potentially be applied to decision-making process for COVID-19 vaccines. I wanted to spend the first of this presentation outlining the key aspects of the influenza annual strain selection process that allows us to get to the end state. And the end state isn't just beginning production of product. It's actually having sufficient product available to meet the demand for that influenza vaccination season.

I then want to spend a few minutes talking about some of the decisions that will be needed in order to reach a similar outcome with the COVID-19 vaccine. Most of you are aware of this general schematic which shows the general process used in the vaccine space to develop and/or replace a new antigen

to an existing vaccine. The process is really the same for any vaccine. It's just -- as was mentioned before, for influenza vaccine this is something that happens on an annual basis, which is a little bit different. What I want to discuss a little bit more then, as we move forward, is focusing a little bit more on influenza.

So, for influenza, overall the process balances that we're looking to do is hold off making a decision as long as possible -- and Kanta did a great job of talking about what happens over time during that course of a year as we work to identify the strain -- and then, on the other hand, needing to make that strain selection decision in time for manufacturers to produce the vaccine. One of the things that I want to mention is that, from a manufacturing perspective, at the time of that strain selection for influenza it's not a cold start.

Because of the well-defined process that we have, manufacturers are often able to do a lot of preparation prior to the actual strain selection decision from the FDA in terms of the composition of

the vaccine. And it's important to remember also in addition to the manufacturing aspects, as Kanta also covered, there's a lot of work being done behind the scenes to select the seeds, characterize them so that once that FDA decision is made about what strains are going to be part of the vaccine, manufacturers are immediately able to start producing vaccine.

Finally, when we think about timelines, it's important to recognize two aspects from this curve. So this curve right here is a seasonal influenza vaccine uptake looking at administrations on a weekly basis. And two important points from this. The first is that as you'll see here, when we look at when the recommendation is made for your seasonal influenza vaccine and when manufacturers start to produce product, which is really they start producing and releasing product in the August timeframe, you still have several weeks before we start entering that peak demand phase, so that's additional time that can be used to produce additional vaccine.

The second thing that's really important to

remember here is that this curve looks very similar year to year. There's some slight differences, but in general, it looks the same. And this represents the demand. From a manufacturing perspective, one of the most important things to understand is what is the demand. And so, by having this known curve that looks similar season to season, they're able to do a lot of forecasting for their production cycle. As we look at the overall process for the annual influenza vaccine production cycle, what pieces come together to make them work?

There's really three main streams here. The first is the production platform. All production platforms right now that are making influenza vaccine really well-described and characterized. Manufacturers have a lot of experience with them. They're all capable of being used in a multivalent presentation. So a lot of similarity -- certainly differences, but also similarities from a general manufacturing understanding perspective. Second is the ability to match the supply and demand situation. So, as I

mentioned previously, there's a well understood demand. There's well understood production timelines and yields from these manufacturing platforms.

And then, when we couple that with the excellent surveillance system that was discussed earlier, manufacturers are able to time their production well so that they have that vaccine ready for that fall manufacturing campaign. Finally, we have a very well-understood regulatory policy pathway that allows manufacturers to prepare well in advance, understand when they need to start manufacturing and what they need to make sure that their vaccine is licensed in the late summer in time for the fall influenza vaccine campaign.

So, as we shift gears a little bit, let's look at the current COVID vaccine landscape and what factors impact potential timing of ability to produce vaccine to support a fall vaccine campaign. So, as was previously mentioned for the COVID-19 vaccines, we have a lot of differences between platforms. And those platforms, we have various levels of experience

manufacturing COVID with different COVID antigens, as well as just manufacturing in general. Even within the same platform it's important to remember that there a lot of differences. Differences include the manufacturing capabilities but also potential things such as global demand, global orders that need to be filled, and also the yields and the amount of product that's used per dose.

So all of these are going to have a significant impact on when a manufacturer needs to start manufacturing in order to have that product available in the fall. Finally, other factors that will drive production timelines, level of testing to support these strains, does the manufacturer have seed banks available for the selected strains -- I'll talk about that a little bit more -- the ongoing need to produce prototype vaccine to vaccinate naïve individuals, and finally, how much risk, if you will, is a manufacturer willing to take on prior to have a firm decision on what the strain composition is going to be for the vaccine.

I'm going to talk a little bit more about a couple of these key objects here in this next slide. What I want to do briefly is a little bit of scenario planning or look at this from an example's perspective. We get back to the original question. When do you need make a decision on a strain selection in order to have enough product available in the fall for a vaccine campaign? Let's make as an example two different manufacturers. Each manufacturer right now -- manufacturers are doing a lot of work looking and characterizing different strains, making different banks, doing different clinical trials.

Let's say one manufacturer selects strain A, and they're doing some work now. And then another manufacturer selects strain B, and they're doing some work. Let's say the decision is made next week that the decision -- the vaccine composition would be strain A and that in order to get a BOA or an EUA for that vaccine you need to do a clinical trial. The company that selected strain A and did the work on strain A, they're going to be in pretty good shape. They're

going to be able to take that data that's coming down, use that for their filing, and be comfortable moving forward with large scale production.

The developer that focused on strain B now all of a sudden is left really far behind. So when you think about the timeline needed to make a seed, to generate Phase I clinical trial data, in the best-case scenario you're looking at 16 weeks. And so you look at the calendar, and you can see that means that data readout happens in late summer, which if the decision is not to go ahead with large scale manufacturing till that data comes down, will be too late to have product available for an early fall vaccine campaign.

That's just one example of the many decisions and many factors that are going to come into play when we think about the timing to make a decision around which strains are going to be a component of the vaccine. So I wanted to wrap things up with these last couple of slides here, expanding particularly on the regulatory factors, besides the strain change, that will impact timing of vaccine availability. This

figure here identifies six key decisions. By no means is this an exhaustive list. These were just some of the things in our experience to date that we think are particularly of importance.

I want to call out three in particular. The first will be in terms of who decides the strains and how many strains for the vaccine. So getting back to the earlier discussion around influenza, currently there are trivalent and quadrivalents vaccines licensed with the regulatory authorities determining which strains are in each vaccine but individual manufacturers determining if they have a trivalent or a quadrivalent vaccine. When you think about COVID-19, obviously if there's a decision to go with a bivalent product, that has significant impact on product availability and timing of that availability.

So it's very important for manufacturers to know early on where will they have flexibility to decide their presentation and where will it be determined by the regulatory authorities. Second thing to look at is, as we think about an indication for a

fall boost, what's going to be the indication or the recommendation for individuals that have not yet received either the primary series or the first boost? Are they going to be recommended to receive the vaccine in the fall that's recommended for people that are receiving their fourth or fifth dose? Or will they be recommended to receive the current prototype of vaccine strain? From a manufacturing capacity perspective as well as planning, that's going to be a really important decision.

And then, finally, the third thing is how will the label read in terms of timing for that recommendation of the fall boost? And what I want to do is just circle back to a slide I showed earlier with another figure overlaid. So, as I mentioned, in red you have seasonal influenza, vaccine demand over time, and then what you have in blue is what we saw in terms of vaccine demand for the COVID boost last fall. And, as you'll notice, with that -- you'll recall with that COVID booster recommendation, there was a recommendation that -- essentially the kind of

recommendation tens of millions of people were eligible for that boost.

So that caused a very rapid increase and uptick in people receiving their vaccine, meaning that you had to have significant amount of product available at the time of that EUA and ACIP recommendation, whereas, the influenza seasonal recommendation and label, which is a little bit broader in terms of not fitting a specific date relative to your previous vaccination, you tend to see that more gradual lead up to that peak vaccination.

And again, from a manufacturing perspective, really important when you look at these curves and there's about a difference of roughly four to six weeks in terms of when you need to be having your maximum amount of product available. And that's looking at peak manufacturing time there in the August timeframe. So understanding what that indication will look like and how that's going to drive uptake is going to be very important.

So, in conclusion, while unfortunately I can't

tell you a specific date by which a strain change decision needs to occur in order to have sufficient product for a fall booster campaign, I hope I've provided some insight into the underlying complexity and the importance of providing insights, guidance and decisions on these various issues as soon as possible. I'm happy to take any questions. Thank you.

**DR. ARNOLD MONTO:** Thank you, Dr. Johnson. Let me lead off by asking you to update us on work that might have been going on already on bivalent vaccines because we keep hearing the suggestion that given the spread between Omicron and some of the other variants we might be considering a bivalent vaccine.

**DR. ROBERT JOHNSON:** Yeah. The manufacturers are working on a bivalent. I think the challenge is that they're not necessarily all working on the same category and the same types of bivalent. And so will they have bivalent data? Are they getting experience with how to make a bivalent product? I think yes. I think though it is important for there to be some alignment around kind of which ones should they be

focused on and which ones should they be looking at.

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

**DR. HAYLEY ALTMAN-GANS:** Thank you very much. I had a question regarding your prediction of the ability of these manufacturers -- I mean, they're not all the same, and they're very variable also with influenza. But if we have two circulating viruses that have the same need -- obviously, we're more seasoned with influenza -- what will be the capacity actually to do both of these? And will there be then a different timeline needed? And then the other one along Dr. Monto's question, rather than these valents, what about a universal or panvalent vaccine that's in the works?

**DR. ROBERT JOHNSON:** Yeah. So, in regards to your first question, if I understood correctly, it was the ability to make a bivalent product?

**DR. HAYLEY ALTMAN-GANS:** No, it's the ability to actually meet the needs for both influenza as well as COVID. So if those circulate at the same time in these countries.

**DR. ROBERT JOHNSON:** So, appreciate that question, so right now we don't envision that will be a challenge. Certainly, there are -- from a supply chain perspective, there are some shared components that, if you look at manufacturing capacity where products are made, and just in general we don't see that as being a concern in terms of being able to produce the necessary products. In terms of the question around the universal product, yeah, I mean, I think that's obviously something that would be great to have. And once that's kind of developed and looked at, then we'll be able to have a better handle on the manufacturing capacity and what that will look like.

**DR. ARNOLD MONTO:** Thank you. Dr. Rubin.

**DR. ERIC RUBIN:** Thanks, Dr. Johnson, and this is really very important to the questions being posed to us today. I had a question about the different technology platforms that are being used now, which are obviously very different from influenza. How does the mRNA technology compare to the viral vector vaccines that are being (audio skip) now in terms of the

rapidity of manufacturing?

**DR. ROBERT JOHNSON:** Sorry, when you say rapidity, could you clarify what you mean by that?

**DR. ERIC RUBIN:** The time to actually having product in a vial.

**DR. ROBERT JOHNSON:** Yeah. So, you know, I think at the top level it's fair to say you can look at the timing of kind of when product came out after COVID was first discovered. Essentially if we look at that sequentially, we see the mRNAs came out first followed by the recombinant protein and then some of the viral vectors. And I think at a top level, we would expect to see something along those same lines continue going forward.

**DR. ERIC RUBIN:** But presumably we've learned something since that time in terms of how most efficiently to manufacture, how to make (audio skip).

**DR. ROBERT JOHNSON:** Correct. The challenge is that these different platforms simply have different regulatory requirements, so some things are -- you can only compress things so much for some of the testing

that has to be done as well as for some of the time needed to identify the best -- you know, do the best strain selection and those types of things. And there's just inherent differences in the platform about how quickly that can be done. So, certainly across the board we have seen, and we will expect to see, increases in things such as yield and efficiency. I think from an overall timeline perspective, again, something could always change, something unexpected, but I would expect kind of that order to be about the same.

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

**DR. CODY MEISSNER:** Thank you, Dr. Johnson. A very interesting problem that you have coming up. I just want to get your thoughts, I guess, about a couple of points. Number one, it will depend on what platform everyone decides to go forward with. That is, if it's a messenger RNA platform, in a certain way that makes it a lot easier than with the influenza vaccines, at least that we currently use, most of which require growth in embryonated hen's eggs. And the point is

that it takes about six months after the seed is selected to make the finished product.

But with a messenger RNA that's going to be a much shorter turnaround time, isn't it? I mean, I think we hear that the pharmaceutical folks can make a new mRNA vaccine in a matter of days, or a week, and will probably be able to fill the vials and distribute that a whole lot quicker than they can with influenza. And the other point is, that would be much safer. Obviously, we wouldn't want any pharmaceutical company to -- or we would hope they wouldn't have to grow up enormous amounts of SARS-CoV-2 because it would present a hazard for some people. The advantage of messenger RNA platforms is appealing from a safety standpoint too, I guess, as well as in terms of speed.

And then the other question that you mentioned and that you alluded to, how will you test these new vaccines? With influenza, we have a reasonable understanding of a serologic correlate of immunity. Probably, even though it's not very good, we can estimate it, and we can't with -- at least right now,

with SARS-CoV-2 vaccines. And so, how can -- I mean, it's going to be so hard to make a new SARS-CoV-2 vaccine and say, oh, yeah, this one works, and we can replace the existing one. So, anyway, I guess a lot of interesting questions confronting you. I don't know if you want to comment on any of those.

**DR. ROBERT JOHNSON:** Yeah, so appreciate that. I'll comment quickly. I know we're running a little short of time, but those are great questions. And so, a couple things, so first, I should point out none of the vaccines, at least the ones that BARDA has supported and currently has EUA, utilized the live virus. Even the recombinant ones that are in development, those are recombinant proteins. Nothing is live virus. So that's kind of the first thing. The second thing, we would expect the mRNA vaccines to be, quote, first out of the gate, if you will. I mean, we have seen that today as we looked with information from other variants.

I think two things to consider is that, one, we do want to be a little careful thinking back to some

of the past influenza vaccine days when we didn't have a lot of -- a limited number of manufacturers. And then if you have one manufacturer go down, has some unexpected issues, you were really in a bad spot in terms -- so you want to have some breath there. The second thing is, while mRNA might be faster to make that seed and certainly get to that production, there's all these other decisions that are going to have an equally important impact. And so, as I mentioned, the need for a clinical trial, those types of things -- those are going to have an equal impact across the different platforms.

So just, again, agree in terms of the speed, but I think there's some of these other things that we have to keep in mind. And, finally, in terms of the correlate, agree. There's a lot of work going on in this space, and there will continue to be a lot of work. I think it is one of the most challenging things you will have to discuss and make some recommendations on I think -- what exactly does that look like because it is such a work in progress.

**DR. CODY MEISSNER:** Thank you.

**DR. ARNOLD MONTO:** Thank you. Final question is from Dr. Cohn.

**DR. AMANDA COHN:** Thanks, Dr. Johnson. To steer away a little bit from the technical questions, I was wondering programmatically how -- the influenza program is mostly private purchase vaccine compared to the COVID program, which has been entirely governmental purchased -- and how the impact on normalizing of transitioning COVID vaccination into the private sector could or may impact the timing of these variant strain changes and other new vaccines.

**DR. ROBERT JOHNSON:** Yeah. So a little beyond my area of expertise. I think in general the decision around the vaccine composition and the timing of availability would not have a big impact regardless of kind of who was paying for the product, which I think is kind of your understanding. When we look at how it's currently purchased and currently provided, again, from just a strain selection determination process, fairly straightforward. There are -- again, not my

area, but I do know that from a commercialization perspective there are a lot of moving pieces that have to be put in place. That would have to be looked at, and again, probably somebody with more experience than I would need to talk to that. But it is a great point.

**DR. ARNOLD MONTO:** Thank you. Do I see an additional hand raised there? Dr. Nelson.

**DR. MICHAEL NELSON:** Thank you. Thank you, Dr. Monto, and thank you for a great, eloquent presentation. Certainly, the challenges and unknowns outweigh our current ability to accurately predict a decent cycle for selection of new strains for a COVID-19 vaccine. There were two important points that you highlighted during your presentation that I hope you might be able to expand on. One is the non-seasonal early demand signal we would likely expect.

If we were to change the strains of the vaccine, there would be a more immediate demand signal from the public for these newer vaccines, unlike what we see with seasonal flu. Thank you for pointing it out. I think it's very important. And you also talked

about the importance of at risk manufacturing by the -- or at least work done towards manufacturing for each influenza seasonal cycle. In this current environment of unpredictability, do you foresee with any of the current platforms, or any of the current manufacturers, an environment where at risk production might not be required?

**DR. ROBERT JOHNSON:** I think it will depend upon the other regulatory decisions. And what do I mean by that? If the decision is that we would like to have product available for a boost in September, okay, and the strain selection decision is not going to be made until, let's just say, beginning of May and if in order to get that license you have to have a clinical trial -- if you're not on your way to that clinical trial by the beginning of May, I think it's going to be very difficult to have, collectively across manufacturers, enough product to meet that demand.

Could be wrong. There's lots of factors in here, but that would be a pretty difficult thing to do I think. And, again, I will just briefly point out, to

my knowledge, all of the manufacturers are doing things in the space. It's more a matter of are they doing -- the question is are they doing the right thing in terms of focusing on the right strains, which I think will probably be the biggest challenge.

**DR. MICHAEL NELSON:** Thank you for pointing that out. Certainly, the challenge of reducing selection to production time and availabilities going to be key to ensure that any changes in the vaccine will actually be relevant to circulating strains and uptick from product once it's made available to the public. Thank you.

**DR. ARNOLD MONTO:** And thank you all. This concludes our morning and early afternoon session. And we've given Mike and his group enough time to get ready for the oral hearings -- public hearings. So we are going to have that, and then we will --

**DR. PRABHAKARA ATREYA:** Dr. Monto.

**DR. ARNOLD MONTO:** -- be starting up again --

**MR. MICHAEL KAWCZYNSKI:** Dr. Monto.

**DR. ARNOLD MONTO:** Yeah.

**MR. MICHAEL KAWCZYNSKI:** Again, hold on a second. Dr. Monto, we're going to have to take a 10 minute break because I have to be able to call in all the OPH speakers.

**DR. ARNOLD MONTO:** Okay.

**MR. MICHAEL KAWCZYNSKI:** So we're going to take a brief 10 minute break. That's just a standard practice. So at this time, studio, if you can, please put us on music and then we will get that started. Is that all right, Dr. Monto?

**DR. ARNOLD MONTO:** That is all right. And after the Open Public Hearings we resume at 2:30.

**MR. MICHAEL KAWCZYNSKI:** Perfect.

**[BREAK]**

**MR. MICHAEL KAWCZYNSKI:** All right. Thank you and welcome back. And now we will hand it back to the chair, Dr. Monto.

**DR. ARNOLD MONTO:** Thank you, Mike. Welcome to the open public hearing session. Please note that

both the Food and Drug Administration, FDA, and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the Open Public Hearing session of the advisory committee meeting; FDA believes that it is important to understand the context of an individual's presentation. For that reason, FDA encourages you the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors.

For example, this financial information may include the sponsors' payment of expenses in connection with your participation in this meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. Over to you, Prabha.

**OPEN PUBLIC HEARING**

**DR. PRABHAKARA ATREYA:** Thank you, Dr. Monto. Before I begin calling the registered speakers, I would also just like to add the following guidance. FDA encourages participation from all public stakeholders in the decision-making processes. Here the advisory committee meeting includes an open public hearing session -- OPH session -- during which interested persons may present relevant information as their opinions of use.

Participants during the OPH session are not FDA employees, are the members of this advisory committee. FDA recognizes that the speakers may present a range of viewpoints. These statements made during the OPH session reflect the viewpoints of the individual speakers or their organizations but are not meant to indicate agency's agreement with the statements made. I would first call upon the speaker, Dr. Jessica Rose, who has a PowerPoint presentation.

Thank you.

**Dr. Jessica Rose:** Hello. This is my third time presenting data in the context of VRBPAC meeting. Thank you very much for having me. The last time I presented on October 26th, 2021, the advisory committee voting members voted 16 to 0 with one extension on the injecting of 5 to 11-year-old children across the united states with COVID-19 products. It's also statistically implausible for the voting to be skewed 100 percent in one direction, and with all due respect, I was left feeling as though I had just spent my time going through an inconsequential exercise, rather than a meaningful democratic process. I've decided to speak again today, however, because even though I have very little faith in the system, I still do have faith in people. I have no conflicts of interest to declare.

Slide three. In preparation for my three-minute presentation today, I read the event materials at the bottom of the FDA online site where the announcements of this meeting is posted. Within the event materials, there are two PDF files posted and

available for download that came to my attention. One is entitled Labor to Allow Participation in an FDA Advisory Committee and the other USFDA Advisory Committee Member Acknowledgment of Financial Interest. At least one of the advisory committee temporary voting members sitting before us today is, in fact, conflicted financially.

That voting member has identified it has a personal financial interest as well as financial interest of his employer, which can be a factor by a particular matter of upholding the committee. The latter financial interest are imputed to him under the Federal Conflict of Interest Statute 18 U.S.C subsection 208. Although no one will doubt that standing judges excellent and unique qualifications and expertise on such matters as seen; the expertise is not in question. The conflict of interest is, in my humble opinion.

The waiver that allows them to be a temporary voting member today was based partially on the fact that, quote, it'd be impossible to replace him. I do

not believe this to be true. There are certain many excellent and exceedingly qualified experts able to serve as a temporary voting member who are not financially conflicted. This, in my opinion, would allow for a more unbiased judging panel standing before us ready to vote judiciously on this very sensitive matter.

In my opinion, in order to honor judiciary responsibility, it should never be the case that expertise can be used as the reason to waive a conflict of interest, financial or otherwise. A conflict of interest by definition means that judgment or decisions could very well be compromised by the conflict. Which is why our government agencies regulate them. If a yes vote means personal and professional financial gain, then why wouldn't one vote yes.

I believe that precisely because of the sensitivity of the subject matter, that it is not serving the public to have conflicted parties as voting members. This is the very same committee that voted to recommend to the FDA to license the Rotashield vaccine

in February (audio skip) '98 that ended up being withdrawn in 1999 due to a proven ongoing deception.

Slide two. My original intention today was to present an update on adverse event data from the VAERS government database to show that the rates of reporting are not decreasing. In fact, they are continuing to increase in the context of the COVID-19 injectable product. I will simply leave you with the summary side. Thank you very much for your time, again.

**DR. PRABHAKARA ATREYA:** Okay. Thank you. The next speaker is Josh Guetzkow. You have three minutes.

**DR. JOSHUA GUETZKOW:** My name is Josh Guetzkow. Yup, thank you. My name is Josh Guetzkow, I have no conflicts. You need to ask yourself, why did only half of all eligible Israelis go back for the second booster? Could it be due to adverse events experienced by them or people they know from previous doses?

Next slide. What you didn't hear about today from the Ministry of Health is a survey they conducted last fall of about 2,000 Israelis three to four weeks

after they received the first booster. The survey asked about adverse events they had experienced.

Next slide. The adverse event rate per million doses calculated from the survey shows that people experienced unacceptably high rates of severe adverse events like Bell's Palsy, hospitalization, and seizures.

Next slide. In September, representatives from the Ministry of Health told this committee that there were only 19 serious adverse events reported to their safety monitoring system following the booster dose, and today they reported 12. But a comparison between the survey results and their monitoring system clearly shows that it is totally unreliable. That it undercounts adverse events by several orders of magnitude.

Next slide. Sizable percentages of people with preexisting conditions reported that their conditions got worse after the first booster. Next slide. A large majority said their adverse event was either new or worse than the previous doses. A

significant minority said their condition was still ongoing three to four weeks later at the time of the survey and that they had sought medical care. The fact that the vast majority of events started within one week of the vaccination and was not spread evenly over the time period strongly suggests they were caused by the booster.

Next slide. The research from Sheba Hospital on the fourth dose corrects for many biases that place all of the large and observational studies on vaccine effectiveness, including the study you heard about to date. Next slide. It showed a very high rate of severe systemic reactions and all signals of benefit were below 50 percent which should make it ineligible for EUA.

Notably, there was no statistically significant reduction in infections or viral load despite a strong antibody response. Could this be due to T-Cell exhaustion? The European Medicines Agency has raised this concern.

Next slide. We now know that the first doses

of these mRNA injections have varied and unexpected effects on the immune system in ways we are only beginning to understand. The effect of repeated doses is uncharted territory.

Next slide. One troubling indicator is that the per dose reporting rate of immunodeficiency syndrome after the third dose is 16 to 21 times higher than for previous doses. These are not like flu vaccines.

Next slide. Approving additional boosters without having solid answers to the questions on this slide would be negligent and only serve to further erode the publics' rapidly waning trust in the FDA and other public health agencies. Thank you for your time.

**DR. PRABHAKARA ATREYA:** Thank you. The next speaker is Dr. Sahin.

**DR. AYGUEN SAHIN:** Thank you. Cover slide, please. Hello, my name is Dr. Ayguen Sahin. I'm the CEO and cancer leader of Cancer Education and Research Institute recognized by the United Nations and today I will be focusing on equality in healthcare for

everyone. I have no conflict of interest to declare.

Next slide, please. As we all know, one size does not fit all in biology and medicine. More vaccines must be made available for the public based on their physiology, medical condition, and personal choice. In this time of technology, this is possible. Taxpayers should be able to receive the vaccine they need.

Next slide, please. Millions of Americans with various health conditions have been left behind throughout the entire pandemic. These people are still unvaccinated and in lockdown for two years now.

Next slide. The data is clear. There's absolutely no scientific reason not to approve Novavax Covaxin, and not to give more attention to Corbevax here in the United States.

Next slide. Novavax, Covaxin, and Corbevax should not be labeled as alternatives. These are proven and robust technologies already used in other diseases. This is exactly what the American people are desperately looking for.

Next slide. Long COVID symptoms are real and horrific, and I predict a severe burden on our healthcare system and economy.

Next slide. Therefore, protein-based vaccines and Virion must be approved immediately. This would be a game-changer in overcoming vaccine hesitancy and to end this pandemic.

Next slide. Biologically, the most effective way to eliminate current and future variants would be the Virion vaccines. There is no time, health, and economy to wait for a pan vaccine to be developed.

Next slide. Scientifically, again, there is no reason not to approve Novavax, Covaxin, and not to give more attention to Corbevax for children and youth here in the United States.

Next slide. A good portion of the world is still unvaccinated. The United States must take leadership in this by immediately approving protein-based vaccines and Virion vaccines. This is critical to end this pandemic.

Next slide. The pandemic is not over for the

unhealthy. Taxpayers want their return of investment and equality in healthcare must be achieved in this pandemic. Thank you for giving me the opportunity to speak today and for your attention to these important matters. Thank you.

**DR. PRABHAKARA ATREYA:** Thank you. The next speaker is Dr. David Wiseman.

**DR. DAVIDE WISEMAN:** Thanks. Can you hear me? Hello? Can you hear me?

**DR. PRABHAKARA ATREYA:** Yes, we can. Go ahead.

**DR. DAVID WISEMAN:** I'm sorry. Please see our written comments. Next slide two and next slide three. Waning and negative efficacy falls below FDA's 50 percent target or 30 percent lower confidence interval before four months. Next slide four. Boosters wane similarly both for BA1 and BA2.

Next, slide five. Fourth dose confidence intervals in Israel go negative. And today's Israeli updated time series suggest a waning trend similar to doses two and three. Next, slide six. The data are

partly consistent with our look at European data, but all-cause mortality should be more reliable. We see limited periods of benefit in the over 60s among periods of all-cause mortality associated with boosting and greater detriment in those younger.

Next, slide seven. We found a similar detrimental association in CDC data. Next, slide eight. Frequent boosting has been questioned in EMA and states it as the last whack-a-mole. Next slide nine. Safety signals with event ratios over flu rates in the hundreds are ignored. Next slide ten. With today's discussion of booster and variant dosing, how are long-term tox concerns allayed by ignoring the gene therapy definition. These are not classical vaccines.

Next slide 11. The toxicity of non-natural nucleosides, especially with cumulative dosing, is raised by BioNTech's founder. Next slide 12. What are the kinetics of the modRNA -- or spike protein? Does it persistence over eight weeks not alarm anyone? Next slide 13. Evidence of reverse transcription to DNA invokes Dr. Sahin's fear of insertional mutagenesis.

Next slide 14. Where are the caner or genotoxic studies? With repeated dosing, what is the risk of insertional mutagenesis from DNA impurities mentioned by EMA?

Next slide 15. Moderna and BioNTech expected to see gene therapy type regulation. Next slide 16. FDAs gene transfer branch has six gene therapy labs researching COVID and a universal flu vaccine. Sounds a little bit like polyvalent COVID vaccines. Next slide 17. FDAs gene therapy committee were asks recently about liver neuro thrombosis and oncogenic toxicity of viral vectors.

Next slide 18. This sounds familiar given that CDC recognize a post-vax multi-system inflammatory system that includes blood, liver, and neurotoxic events. Next slide 19. Is FDA hiding gene therapy concerns in plain sight? How does OTAT and the cell therapy committee opine? Why are FDA excluding its own experts? Next slide, 20. Let Dr. Hildreth ask the sorts of questions he asks about monopurity (phonetic) and NBAT.

Next slide 21. Given the uncertainties discussed today about spring production, don't throw out Ivermectin after this last study whose PI suggests effects lost by underpowering and where 25 percent of subjects missing from a key analysis showed a 50 percent efficacy.

And last slide, 22. FDA's failure to inspire confidence in Nobel gene technology does not portend better pandemic management. Thank you.

**DR. PRABHAKARA ATREYA:** Thank you. The next speaker is Maria Young.

**MS. MARIA YOUNG:** Hello, my name is Maria Young and I'm a severe COVID-19/ECMO survivor. The photo I've shared is me almost exactly a year ago. In October of 2020 we all anxiously awaited the development of COVID vaccines. I was a healthy active 41-year-old doing Bootcamps Yoga and working as the director of conference services. Even with precautions I contracted COVID-19 and became very sick.

After two negative PCR tests and a hospital release, I called the ambulance for myself. My oxygen

was at 40 percent when it should be in the upper 90s. after 12 days at a local hospital, on several types of oxygen masks, I was sedated, intubated, and transferred to the Johns Hopkins Hospital in Baltimore where I was placed on a ventilator and ECMO. ECMO is the most intense form of life support we have and is available in less than ten percent of American hospitals. I was not expected to survive.

Next slide, please. I spent almost three full months sedated and often paralyzed. During my hospitalization I suffered several collapsed lungs, a blood clot, a severe eye injury, several infections, three blood transfusions, drug withdrawals, delirium, demoralization, and my family was unable to see me for almost three months.

I remember nothing from early November until mid-February. I had to relearn to walk, talk, swallow, and to be independent. On the day of my hospital release, my parents and sister received their first dose of the Pfizer vaccine. That same week we lost a close family member to COVID-19 in Ecuador before she

was able to receive the vaccine. I'm happy to say that I am fully vaccinated against COVID.

As a result of my illness, I've started a non-profit called Maria's Miracle, which is dedicated to funding critical care medical training and supporting families and patients facing ECMO treatment or recovery from prolonged ICU stays. I also work as a vaccine advocate with the national non-profit organization Vaccinate Your Family, to increase awareness about the seriousness of COVID and the importance of vaccination.

Next slide, please. I share my story, not to instill fear, but to highlight the risks of this virus and to emphasize that vaccination is our best protection. I never imagined I would be the one to almost lose my life to COVID. As a result of my illness, my life will never be the same. It's my hope my story can be a lesson for others. Nothing in life is without risk. As illustrated by my story, COVID infection can cause serious outcomes and long-term effects regardless of age or health status. Vaccines continue to be our best defense against hospitalization

and severe illness.

To date, according to the CDC, almost one million people in the United States, including over a thousand children, have lost their lives to COVID. We must do everything we can to protect people from COVID by ensuring they have access to vaccines, testing, and treatment. Thank you for your time.

**DR. PRABHAKARA ATREYA:** Thank you. The next speaker is Dr. Doshi. Peter Doshi.

**DR. PETER DOSHI:** Hi. Hello. Hello, I'm Peter Doshi, thanks for the opportunity to speak, and hopefully, you can see my title slide with the financial disclosures. For identification purposes, I'm on the faculty of the University of Maryland and the editor at the *BMJ*. I have no relevant conflicts of interest and my comments today are my own.

Next slide, please. Last November, the *BMJ* reported the disclosures of a list of lower name Brook Jackson, who worked for Ventavia, a contract research company that ran three of the clinical trial sites for Pfizer's vaccine. Jackson alleged that the company had

falsified data on blinded patients, employed inadequately trained vaccinators, and was too slow -- was slow to follow up on adverse events. She provided the *BMJ* with company emails, internal documents, text messages, photos, and recordings of her conversation with company employees.

Next slide. This photo, for example, shows vaccine packaging materials that are only supposed to be seen by unblinded staff just left out in the open. Next slide. An unblinding may have occurred on a far wider scale. Here you can see the document containing the instructions Ventavia staff were given to file each trial participant's randomization and drug assignment confirmation sheet into each participant's chart. This contains unblinded information.

Next slide. Unblinding, as I think everybody knows, creates serious concerns about data integrity. Once this massive error was discovered, Ventavia asked staff to go through each and every chart to take out the randomization and drug assignment confirmation. You can see here, an email from Ventavia's COO reacting

after discovery of the problem. They had not even realized that the drug assignment confirmation contained unblinding information.

Next slide. In the heat of a pandemic, it's not hard to imagine that corners were cut, and mistakes were made. Some mistakes are benign, but others carry serious consequences to data integrity. One hopes Ventaiva is an extreme outlier, but we need more than just hope. We need evidence that the data were dealt with properly. We need regulatory oversight. But despite whistleblower Brooke Jackson's direct complaint to the FDA; FDA never inspected Ventavia. In fact, FDA only inspected nine of the trials 150-plus sites before approving the vaccine. Just nine sites. And Pfizer continues to use Ventaiva for trails.

Next slide. What about Moderna? FDA had over a year and inspected just one -- one -- of the trials 99 sites. How can FDA feel confident in the Moderna data based on a one percent sample? Next slide. Data integrity requires adequate regulatory oversight. Trustworthy science requires data transparency. It's

been over a year, but anonymized participant-level data remain inaccessible to doctors, researchers, and the public.

The public paid for these products and the public takes on the balance of benefits and harms post-vaccination. The public has a right to data transparency and FDA has an obligation to act.

Thank you very much.

**DR. PRABHAKARA ATREYA:** Okay, thank you. The next speaker is Dr. Brianne Dressen.

**DR. BRIANNE DRESSEN:** Hello, my name is Brianne Dressen. I have no relevant conflicts of interest. For transparency, I am a co-founder of React-19.org, a non-profit made by the COVID vaccine-injured for the COVID vaccine injured and we are dedicated to the advocacy and healing for those suffering lasting adverse events. I experienced a life-altering reaction after my one and only dose of AstraZeneca in the clinical trial here in the United States.

Because of my adverse event, I was not able to

get the second dose. I was unblinded and dropped from the trial. My access to the clinical trial app was deleted. In the *New England Journal of Medicine*, it mentions that these cases are followed for up to 730 days. I was last notified from the clinical trial company on day 60. I wrote to the *New England Journal of Medicine* about the matter and Dr. Ruben who is on this committee declined to publish my letter saying that one case in a study of tens of thousands would have little effect.

You can see my list of debilitating symptoms here, first slide. While I am improving, I still struggle with at least half of these symptoms more than a year out. My life will never be the same. The vaccine has robbed me of my health.

Next slide. Because of the vaccine injureds repeated cry continue to fall on deaf ears at the FDA and the drug companies, and because the medical community refuses to acknowledge and treat us because of the silence from these companies and the FDA, our small, injured community has suffered the loss of those

who have taken their own lives as a result of months-long suffering.

These are mothers, sisters, daughters, sons, fathers, and friends. These are not numbers, these are people. No support from their medical teams, no support from the government. They died alone. Next slide. Here's a list of the insurmountable barriers which exist today that block our access to access to early intervention measures and to help those who are now chronically ill. The column on the left are the compounding factors that completely eliminate the proper flow of information to the research and medical communities.

But there is hope. The column on the right are the solutions. You who are here in this meeting today, hold the key to open the door to provide hope and healing to those who are hanging on one day at a time.

Disclose and collect the data on potential adverse-related events. Like MISV, neuropathy, and tinnitus. Give the green light for research to start.

German health insurance agencies have already established the burden on the healthcare systems due to the high rate of COVID vaccine-related adverse events. Revamp the vaccines to remove the spike as an antigen. FDA it is your responsibility to ensure the safety and efficacy of these vaccines.

We are the clear evidence and living proof that there are questions regarding safety. You have ignored the repeated cries of those injured by the vaccines and your silence is deafening. Thank you.

**DR. PRABHAKARA ATREYA:** Thank you. The next speaker is Alexandra Robinson.

**MS. ALEXIS ROBINSON:** Hi, thank you for having me. Yes, my name is Alexis Robinson, I'm 37 years of age. After I received the COVID vaccine, I was diagnosed with tinnitus, Endolymphatic Hydrops, glaucoma, HS, peripheral neuropathy, and myalgia.

Next slide, please. My symptoms include tinnitus, shortness of breath, chest pain, severe neck and shoulder stiffness and pain, head pressure, dizziness, nausea, tingling in the feet, severe calf

pain in both legs, internal tremors, body aches, glaucoma, fatigue, stomach pain, ear pain, and fullness.

Next slide, please. Before the COVID vaccine, I was happy, full of life, and on the right path. Able to get out and walk and actually enjoy sunny days outside. I enjoyed calling to speak to my family on a regular basis. That all changed April 7th, 2021, when I received the COVID-19 vaccine. I thought I was doing the right thing by receiving the COVID vaccine to protect myself, my family, and others.

It has been a horrible nightmare ever since that day. I'm in constant agony and pain. Simple tasks like grocery shopping can be unbearable. I have so many side effects that I would have never imagined were even possible and that were never mentioned by Pfizer. Now 90 percent of my time is spent inside.

I've had doctors be both be very rude and dismissive and even some that have walked out me if I even mention that my symptoms were caused by the COVID vaccine. They aren't even willing to explore doing

further testing or treatment. Dealing with these side effects have been overwhelming every day -- an everyday struggle.

Next slide, please. When will the COVID vaccine injured people be acknowledged and treated? It is of the upmost importance for COVID vaccine injuries and adverse reactions to be acknowledged in order for us all to receive the best care, thorough testing, and ultimately be believed. Time is of the essence. None of my physicians have reported my case severe. This is because they don't have all the factual information that's being withheld to fully understand the severity of our cases.

That critical data supports the evidence of our injuries. We need immediate, sufficient, and adequate care for these gravely devastating effects in order to stop the progression of these illnesses caused by the COVID vaccine. The release of data and acknowledgement of vaccine injuries will not only allow us to receive the correct treatment in a timely manner, but it will also open doors to more research into the

best possible ways on how to treat us and to help prevent future injuries.

Those injured by the COVID vaccine involve all age groups who are suffering and being continuously silenced. Would you silence your children, your relatives, your grandparents, your family, your friends, your loved ones, and let them suffer? Help save lives. FDA, release the VAERS data. Thank you for your time.

**DR. PRABHAKARA ATREYA:** Thank you. The next speaker is Sarah Gleason.

**MS. SARAH GLEASON:** Hi everyone, my name is Sarah Gleason, I'm 42, and I was thrilled to get the Moderna vaccine. As a massage therapist of 22 years, I decided to shut down my thriving business due to fear of catching and spreading COVID-19. I suffered greatly for it, but I resolved not to reopen until I could ensure everyone's safely.

I'm a democrat and absolutely pro-science. I was excited to rebuild my business after being vaccinated. Instead, I received my second shot of

Moderna on April 2nd, 2021, and my dreams of rebuilding came crashing down. The injuries it caused persist a year later with no end in sight. Many of my symptoms are listed on the slide, but this is not all of them.

Doctors I saw originally didn't know what to do with me. I've learned I was one of the lucky ones since they, at least, treated me kindly. Even though it all began when I got the shot, I was even in a bit of denial because vaccine injuries are just anti-vax nonsense, right? I was dead wrong and have been choking on humble pie ever since. If it wasn't happening to me, I wouldn't believe me either. Doctors are simply not being educated about vaccine injuries and the damage they're doing to us, due to this lack of knowledge, is staggering.

Trying to live with these symptoms is hard enough; to not be believed by doctors, family members, and friends as your once strong and healthy body deteriorates; the damage this can cause is immeasurable. Science demands the totality of the data with transparency, and this is clearly not happening.

Science is not being carried out when variables are being ignored. I had to advocate for myself while experiencing some intense symptoms, combing the internet for information I didn't know was being withheld. It took me almost 11 months to even be seen by a neurologist.

Luckily for me, this particular neurologist has been studying vaccine injuries and has other patients like me. My medical chart finally clearly states my symptoms are vaccine induced. So, because my reactions are not being properly researched, she says she has nothing more for me than quote/unquote band aids. She says that maybe if doctors had tried to help me early on, maybe the worst of it could've been prevented.

Instead, the doctors I saw at the beginning just told me to wait, and wait, and wait some more. This was their expert medical advice. By July, I had gotten so much worse and now I wonder what might've happened if they'd only been informed of the type of reaction I was having. I don't want this to happen to

anyone else. To be hurt and left to fend for themselves. I just want my life back.

I can't socialize much, I can't exercise, I have no way of making an income. Even if I felt well enough, I can't get a booster; so where does that leave me? If I do recover -- which no one can tell me if I will or not -- how will I work safely? The CICP and VICP are supposed to support those who have been injured by vaccines. They have not helped any of us. I don't claim to know the right answer, but I know you have the power to change this. To help us get our health, credibility, friends, family, and financial security back. And who knows what medical discoveries lie inside our bodies. Aren't you curious?

I still stand with science, and I still believe the government and the medical community is capable of doing right by us, but it all starts with you simply doing your job. Thank you so much for your time and consideration.

**DR. PRABHAKARA ATREYA:** Thank you, so much. The next speaker is Karen Discoll.

**MS. KAREN DISCOLL:** Thank you. Hello. I'll start with a little bit about me. I am married and we have two grown daughters and four grandkids. I've worked as a registered nurse for over 30 years. I have lived an active, healthy lifestyle with no health concerns. None. I trusted the government who repeatedly said the COVID vaccines were safe and effective; so, I took them.

Shortly after the second Pfizer, my health and my life seriously changed. The slide shows most of my symptoms I've had and/or still have. Many of them are similar to other vaccine injured and the COVID long-haulers. I'll describe only a few. My daily headaches were sharp and intense, unrelieved by over-the-counter medication. Brain fog left me unable to process information. At first unable to do even simple texting on my phone. Noise and activity caused overstimulation that I just could not handle.

The neurologist said my symptoms were very similar to a traumatic brain injury. I had tremors inside my chest, it felt like a cellphone that I

couldn't turn off. I had adrenaline dumps, which left me in a constant state of fight or flight and unable to sleep. The POTS symptoms raised my heart rate to 140 simply by standing up.

At night, I would literally crawl to the bathroom to avoid this. I somehow managed light cooking and dishes by sitting in a chair. The fatigue is overwhelming. Activity is limited because I easily become breathless, and activity causes my symptoms to get worse. This has been very disabling; I've been unable to work now for seven months.

I've been through a revolving door of physicians without answers. Three of them did acknowledge my symptoms were a result of the vaccine, but they didn't know how to treat me. Basic diagnostics were coming back with only slight abnormalities or normal values, until recently. I underwent some specialized blood tests showing blood vessel inflammation and abnormal platelet activation.

The platelets caused the blood clots. I will be seeing, yet another, specialist very soon. Our

United States healthcare system is not addressing the vaccine injured but instead seems to be sweeping us under the rug. Where is the ethics in this? I'm not an anti-vaxer. This vaccine has injured me, and many others, and we need help now, not in five years. For those of us going through this hell, we don't know what will happen to us over time.

Some have committed suicide. In Europe and Japan, their scientists are addressing the vaccine injured and actively researching to find answers for them. We need you to step up, we need you to do the same, and hopefully collaborate across the globe to find solutions to help us. That's all I have. Thank you for the opportunity and please, please take our comments to heart.

**DR. PRABHAKARA ATREYA:** Thank you. The next speaker is Ms. Amy Fischer.

**MS. AMY FISCHER:** Slide one, please. My name is Amy Fischer. No conflicts. I am not now, nor have I have ever been an anti-vaxer, but I am here to share with you that it is believed I was harmed by the Pfizer

COVID vaccine. My new rheumatologist, a highly esteemed professor of medicine, believes that I likely had an autoimmune reaction to vaccination and consequently developed autonomic dysfunction mass cell disorder and MECFF. Prior to the vaccine, I was completely healthy.

Next slide. Go two slides ahead. I lost my mom to COVID in January ’21 just days before here memory care was to receive the vaccine. So, when my turn came, I eagerly stuck out my arm with tears in my eyes. Next slide. I didn’t have an immediate reaction, but weeks later was overwhelmed by intense fatigue. When I suddenly felt a burning pain in my lower legs and feet, an eight-month long grueling workup began.

As I waited for tests and pleaded to see doctors, my condition worsened. No one seemed to know what was wrong with me and I got no care. Please, next slide. My neurologist believed I might’ve developed long COVID from breakthrough infection, but a negative nucleocapsid test ruled that out. I brought up the

vaccine with a few doctors. Most said something to the effect of, "It is possible, but we don't have any data." We don't have data.

This has been an incredible nightmare. It's been almost a year, and I can no longer do normal things. I cannot be upright for very long. I get easily winded with mild exertion and become incapacitated if I try to do anything more involved. I still have burning, tingling, vibrating pain in all four limbs. Buzzing in my ears.

I'm learning to accept that I may be permanently damaged. I have not worked in almost a year. Now it took me eight months of relentless advocacy and long-distance travel to find doctors who are just now starting to diagnose me. I will always wonder; had I been treated aggressively in the beginning with things like corticosteroids and IVIG would I be fine today? The NIH was studying people like me since January '21; why did my doctors not know?

Now, you could say my illness is coincidence, but I know there are tens of thousands like me because

it's a small internet. Janet Woodcock told me in an email that you were seeing symptoms post vax very similar to post COVID, but we are excluded from long COVID clinics and long COVID studies.

I have not yet reported to VAERS because doctors won't do it and I'm still waiting for POTS assessment. I will report the word is you are not following up. Do your job FDA. How can you be talking about new vaccines until you followed up on VAERS report? Until you've released data, we are invisible to those who should be helping us, and this is very harmful. Thank you so much for listening. I hope you take it to heart.

**DR. PRABHAKARA ATREYA:** Thank you. The next speakers do not have any PowerPoint presentations, so we'll start with Dr. Rituparna Das.

**DR. RITUPARNA DAS:** Thank you. My name is Rita Das and I'm a clinical development lead at Moderna. As an infectious diseases' physician, and a vaccine developer, I am humbled and privileged to be part of the team contributing to this effort to bring

forward safe and effective COVID-19 vaccines. To date, over 75 million people in the U.S. have been vaccinated with the Moderna COVID-19 vaccine, or Spikevax, since it was authorized for emergency use in 2020.

42 million of these people have also received a booster dose. The trajectory of the pandemic has continued to challenge us. Once the Omicron variant emerged, we observed a wave of breakthrough infections with Omicron, although protection against severe disease was maintained. Neutralizing antibodies against Omicron are detected after the primary series of the Moderna COVID-19 vaccine and substantially increase after the booster dose.

But real-world data has shown that vaccine effectiveness against Omicron infection declines over time to less than 50 percent at 60 days or more after the booster. This leaves people who are most susceptible to poor outcomes from COVID-19 vulnerable. We support the agency's authorization of a second booster dose of our COVID-19 vaccine for individuals 50 years of age and older, as well as those who are

immunocompromised. This will be an important tool to extend the duration of vaccine protection while data with variant matched modified vaccine candidates are generated.

Moderna began clinical trials with booster doses of variant matched candidate vaccine such as Beta and Delta, as well as combination of variants in the spring of 2021. To date, approximately 4,500 trial participants have received modified vaccine candidates, including a bivalent vaccine targeting both the Omicron variant, as well as the original strain. We look forward to sharing these data on the modified booster vaccines with the agencies soon.

By vaccinating with an mRNA sequence closer to the currently existing variant of concern, we hope to improve neutralizing antibody titers and thereby extend the duration of protection with booster doses. We thank the agency for the forward-looking discussion today on the long-term strategy for booster doses. As the pandemic continues to evolve, Moderna is committed to pursuing rapid development of variant-adaptive

vaccines that have the potential to provide broader and more durable protection against emerging variants of concern. Thank you very much.

**DR. PRABHAKARA ATREYA:** Thank you. The next speaker is Mr. Matt Crawford.

**MR. MATTHEW CRAWFORD:** Hi, my name is Matthew Crawford. I report no conflicts of interest. Thank you for inviting me to speak. There is currently no transparent data whatsoever showing efficacy of the experimental COVID-19 injectable products. We were promised transparency, but the FDA still fights the release of the vaccine trial data in court. That data is necessary to determine why so many more people in the treatment arm were excluded from analysis.

These exclusions completely overwhelm all efficacy computations. To this day, Brook Jackson's reports of protocol deviations, trail unblinding, and data falsification go ignored by the FDA and CDC. These trials never met basic standards of evidence. Neither do the published retrospective studies. Buried in the supplement of the study by Noah Dagen (phonetic)

and colleagues is an incorrect set of calculations that fail to adjust for a serious bias that the study acknowledges and then downplays.

Professor Mark Reader demonstrated that the study methodology could make a null saline solution achieve a 72 percent efficacy rate claimed by the study authors. Professor Norman Fenton has shown that delays in reporting a mortality can generate short-term appearances of efficacy where none exists. It is noteworthy that this illusion would appear, like rapidly waning efficacy over time, which is exactly what authorities have been reporting in order to encourage booster shots.

In another study in the Israeli population, Hauth et. al (phonetic), the use of short-term intervals of measurement can substantially exacerbate this or other biased effects. The study authors failed to make an obvious risk adjustment in their base unit of person days and most of them reported conflicts of interest in the form of Pfizer equity or options. The CDC now admits to withholding select data from the

public. This admission called all vaccine summary surveillance data into question.

A CDC study from the vaccine safety datalink team concludes that the vaccinated somehow died up to 72 percent less often than the unvaccinated by non-COVID causes. This absurd result confirms the existence of statistical sieves in surveillance analyses. Whistleblowers noticed higher rates of illness in the DMED. The DOD claimed these results were due to a glitch, however, reference data published in the medical surveillance monthly reports was substantially manipulated prior to the May 2021 publication. There are still highly concerning vaccine safety signals, and it is hard to believe that neither the CDC nor DOD noticed any problem with the data for a full nine months.

When vaccines rolled out, every nation in Europe saw spikes in COVID case fatality rates equivalent to over 1,000 extra COVID deaths per million doses delivered. An analysis of Massachusetts data found similar results. In line with those

calculations, a large German insurance company declared that vaccines killed tens of thousands of Germans. Among nations, there are clear positive correlations between vaccination and both COVID-19 case and death rates. These rates rose soon after vaccination programs began in nearly every nation.

The experimental gene therapy campaign is dangerous and unscientific. All facts presented in this talk are sited at the round end of the year sub staff. Have a lovely day and remember antibodies are like electrolytes.

**DR. PRABHAKARA ATREYA:** Thank you. The next speaker is Ms. Kim Witsak.

**MS. KIM WITSAK:** Good afternoon, my name is Kim Witsak, and I'm speaking on behalf of Woody Matters, a drug safety organization started after the death of my husband due to an undisclosed side effect of antidepressants. We represent the voice of families who live every day with the consequences of a flawed drug safety system.

I'm curious exactly why are we meeting today

to discuss the future of boosters, when last week the FDA just went ahead and authorized a fourth shot without the advisory committee input. And why did the FDA authorize booster number two for those over 50 years old even though Pfizer only asks for 65 and older? What a gift these extra 15 years must mean to Pfizer's bottom line.

I hope committee members feel some outrage, as I do, about another FDA decision being made behind closed doors when we were promised an open and transparent process. Over a year ago, the public was told that these rushed-to-market novel mNRA vaccines were over 95 percent effective and stop the spread of the virus.

Follow the science, by March Pfizer quietly started studying boosters and had the data showing waning efficacy all before the Delta variant. But they didn't tell anybody about this until their preprint was released in July. Meanwhile, we, the public just got the dictates. Get fully vaccinated to end the pandemic. Now get boosted to end the pandemic. Empty

slogans to hide the reality that officials are making it up as they go.

The latest, a fourth shot, and already FDA's Dr. Peter Marks is hinting that we'll most likely need a fifth shot in the fall. While the completely efficacious narrative has changed significantly over time, the completely safe message has remained unchanged. Despite the historical high numbers of Bayers reports. Last year, over a million adverse events were filed with over 2,000 deaths. Why isn't this committee, the FDA, mainstream media, and the medical establishment wanting to take an active interest in investigating the injuries, deaths, and increases in other diseases post-vax before we rush into whatever halts transmission or stop respiratory viruses doing what viruses do? We need to stop hiding behind emergency use authorization. We are setting a dangerous precedent of inadequate evidence being used to justify widespread and regular ongoing vaccinations.

Worse yet, schools and employers are using these recommendations to mandate the vaccines putting

our children and adults at risk while not reducing infections. The use of EUA for this fundamentally flawed product is poised to cement a regulatory precedent that will further destroy public's confidence for years to come.

Let's stop making predictions about people's health. Insanity is doing the same thing over and over and expecting a new result. Thank you so much.

**DR. PRABHAKARA ATREYA:** Thank you. The next speaker is Rotem. Ms. Rotem. Rebecca Rotem.

**MS. REBECCA ROTEM:** Hi, my name is Rebecca Rotem. I have no known conflicts. Thank you for allowing me to speak today and for all of your work on vaccines.

I have a 12-year-old son who is fully vaccinated with 2, 30 microgram doses of Pfizer and who also had a COVID infection at the end of February 2022 with documented PCR results. My son is now being required by his beloved Jewish sleepaway camp that he's attended for the past five years to get a booster shot to attend again this summer.

I'd like to be an informed medical consumer, so before he gets the booster, I really would like to understand the risk and benefit data on booster shots in healthy 12-year-old males who are fully vaccinated and have had COVID. I would also like to understand what protection does two doses plus a booster give a healthy 12-year-old as compared to two doses plus a documented COVID infection.

Since they're requiring the booster, I have asked the Union for Reformed Judaism, or the URJ, for the data I'm seeking, and their medical team contact tells me it does not exist. As background, the URJ is requiring all attendees of its 15 youth summer camps to be up to date on shots according to CDC guidelines, with no exemptions from a booster for campers ages 12 and up who are fully vaccinated plus have had a documented COVID infection.

I understand other summer camps have similar booster requirements as well, in addition to colleges in the Northeast and on the west coast. Nearly all of which are requiring the booster and not allowing

exemptions for prior infection. To be clear, I'm not opposed to getting my 12-year-old son a booster if the information I am seeking exists, and the benefits and risks, including myocarditis, for example, in fully vaccinated adolescent males with prior COVID infections justify a booster shot.

But I'm struggling with doing it in the absence of the data which would enable me to do it with informed consent. I imagine this topic is relevant for many other parents as well, considering how many kids came down with Omicron. Does the risk and benefit information I am seeking exist? If not, should organizations be allowed to require this third dose of a medical product? In my experience, these organizations are not conducting their own research, rather consider their booster requirements to be in line with current FDA and CDC approvals and guidance.

Therefore, I think clarification from the FDA would go a long way. Thank you for clarifying the FDA's position on booster requirements for adolescent males who are fully vaccinated plus have had a

documented COVID infection. Thank you.

**DR. PRABHAKARA ATREYA:** Thank you. The next speaker is Andre Cherry.

**MR. ANDRE CHERRY:** I report no conflicts of interest. My name is Andre Cherry, I'm 22 years old, and I was injured after taking Moderna's COVID-19 vaccine. Before this, I was a published author, an artist, musician, an active member in my church, family, and community. On my way to achieving my bachelor's degree in English.

Beginning only two hours after my vaccination, I progressively lost control over my life. My limbs and body parts jerked, contort, and become rigid or flaccid on their own. My eyes and mouth shut tight and cannot be opened of my own volition. I can't tell when I wake up in the morning if I'll be able to walk or see, feed, or bathe myself. I only know I will face trouble resulting from my injury. I sleep on the first floor of my home in a hospital bed, and I no longer can use stairs unsupervised.

My mother and brother have been sleeping on

couches near me out of concern for my safety. I now possess a handicap placard and a wheelchair which I frequently use. I can barely leave my home except for medical or religious reasons, and even then, my family has to carry a bookbag full of safety equipment to make sure I don't fall or injure myself.

For nine months, I and my family have relentlessly pursued diagnosis and treatment only to be met with apathy, sarcasm, and condescension from most of the medical community, affiliated personnel, mainstream media, and society at large. Rather than provide a much-needed follow-up and resources for treatment, I often refer to the *Psychology Today* magazine or offered multi-state travel to find help.

When asking for understanding from a doctor about the vaccine side effects, since you the FDA are not releasing this data, I was told that, and I quote, we don't know how aspirin works. My medical care has been continuously impeded due to your unwillingness to make public the facts about the mRNA technology of this vaccine; which Dr. Malone himself stated to have

cytotoxic properties. This dearth of information robs doctors of the knowledge they need to accurately diagnose and care for vaccine-injured patients such as myself.

You created a social media toolkit, to quote, fight vaccine hesitancy. But it seems more likely that you're concerned with fighting public descent. This country was founded on the idea that we the people should be free to make informed decisions for ourselves. How can free people make free decisions if after every controversy there's a coverup? How can you expect us to trust you when you don't trust us with accurate information? How can you say you care, when you turn away those who come to you for aid? Time and again you admit to (inaudible) harm to the American people, exchanging their health for profit.

Obesity, heart disease, and cancers kill more than anything else because you pedaled processed sugar, tobacco, and the scientifically unfounded food pyramid. Proverbs 3:27 commands you to not withhold good from those to whom it is due, when it is in your power to do

it. We are not acres of skin to be harvested and experimented upon. We, too, are the free people of the United States of America and we demand fair treatment, justice, and equality as is our God-given right. thank you for your time.

**DR. PRABHAKARA ATREYA:** Thank you. The next speaker is Ms. Tanya Grisham.

**MS. TANYA GRISHAM:** Hello, I am Tanya Grisham. Before my Pfizer vaccine on July 29th, I was a healthy 48-year-old with no medical problems and on no medications. I helped my husband with his business, I worked, I ran the household, volunteered, vacationed, and I had a social life.

After my Pfizer vaccine, I quit social functions because of revolting, painful, hyperacusis. I lost 30 pounds in less than three months. I had diarrhea, excessive sweating, and barely got three hours of sleep a night. For over two months after vaccination, my head and neck pain were compounded with brain fog and paraesthesis, inability to stand, vision changes, and hair loss. I had to force myself to do

basic daily functions.

I honestly thought I was going to die. This experience has been hell. My 21-year-old son had to put his life on hold and move home to help me. I have been so ill that I forgot my 20th wedding anniversary. My husband didn't care that I forgot our anniversary, he held me as I cried and told me it was okay. It took months of doctors visits and $8,000 in medical bills, but I finally had three doctors confirm that I am, in fact, suffering from vaccine side effects.

I don't have any answers to when, or if, I will ever fully recover. I miss my former life. I'm begging the FDA to do your job and acknowledge the injured. You've known we exist. The medical community should be aware of us. We are desperate for treatment. There seems to no effort in researching us. Just last month, three members of our community committed suicide because they could no longer live with their debilitating side effects. Our lives matter. We should not be expendable. We should not be abandoned in our time of need.

Thank you for your time.

**DR. PRABHAKARA ATREYA:** Thank you. The next speaker is Jasmine Walker.

**MS. JASMINE WALKER:** Hello, my name is Jasmine Walker. I have no relevant conflicts of interest. Today marks 8 months and 3 days post one dose of Pfizer vaccine. The nightmare that I would have never imagined would happen just by simply trying to do the right thing. I've been to multiple ER and doctor visits with no help or knowledge on what to do with us injured.

Now I am suffering from an autoimmune disease, neuropathy, insomnia, and neurological issues. So many other side effects mostly dealing with the brain. From tremors, brain fog, and unexplained lesions. Previously healthy, 33 years old, single mom of two special needs children who solely depend on me. This experience has been debilitating and ongoing which has caused me to almost lose my job and accumulating so many medical bills and not receiving any assistance from the government or health systems.

People are losing their life due to these vaccines. Some of us are losing everything we've worked so hard for because these injuries are debilitating. These side effects are not even being mentioned as being any of the side effects. We're being swept under the rug and unheard. We need help, we need to be heard, and we need for people to be informed on risks that are associated with these dangerous vaccines.

Please help us, we need to be heard and acknowledged. I'm here today to be heard and for so many others who are injured, and for our children. Please don't ruin their lives with these vaccines that are not even doing the job. We are being ignored. We need you to do your job and to please hear our cries. We are pleading for you to hear us and all of us injured who did our part to keep everyone safe are suffering just as we did our part to help not spread this deadly disease.

We need the FDA and medical community to help us injured from these debilitating side effects.

Please take us seriously. We need you now more than ever. We are in pain, and we need to be heard. We need our lives back. This new life I would never wish upon my worst enemy. I don't want another human being to suffer like us injured have been suffering every single day. Every single day we wake up it's another day we wake up thankful that day that others did not -- who's also tried to do the right thing. Where there are risks, we should have choices, and at the moment that is not being honored.

This was not supposed to happen, and it could have been avoided and it needs to be. The data was known and ignored which is now why so many are injured and could've been avoided. Thank you for your time.

**DR. PRABHAKARA ATREYA:** Thank you. The next speaker is Mr. Matt Matlock.

**MR. MATTHEW MATLOCK:** Hello, my name is Matthew Matlock. I have no financial conflicts. These are my own words. I'm 38 years old, a combat veteran, and father of two young girls. And going into the last summer I was in the prime of my life. I was a top

performer in a large technology firm in the bay area and at the peak of health and fitness having just completed a half iron man. All of that changed after the second dose of the Pfizer vaccine.

I spent the first two and a half months either in the ER, at doctors appointments, or in bed. I was ignored, gaslighted, and told there was no way the vaccine caused my issues. Thankfully, I'm stubborn and kept searching for answers, until I found physicians who would listen and were willing to admit that anxiety was in fact not the cause of my heart inflammation, mass cell issues, radically varying blood pressures, tachycardia, gray skin tone, purple hands and feet, neuropathy, and Epstein Barr reactivation.

I'm not going to compromise the rest of my time on this call sharing with you what an incredibly frustrating experience this has been and how mainstream medicine has completely failed us. I choose to spend the remainder of my three minutes pleading with you to consider the following.

Number one, research and diagnostics. The

same old bloodwork and scans aren't cutting it. We need to think outside the box, and fast. Why were we affected when others weren't? What markers can we identify that will facilitate a diagnosis? These are some of the questions we need answers to. We did our part, you assured us this was safe, we are suffering. It's time the government stepped up and put money and resources towards this effort.

Number two, treatment. The leading free options that have shown the most promise are Bruce Patterson's cytokine and inflammation treatment, Razio Patore's (phonetic) triple threat of anticoagulant, antiplatelet, and ASA, and Dr. Jaeger's Help Apheresis. Please connect with these groups to learn more about their work. Come up with a plan to create a coalition to connect groups like these and mainstream institutions like the Mayo Clinic.

Number three, compensation. To date, CIPC has compensated zero claims. People are losing their jobs, their insurance, their house, and are in debt hundreds of thousands of dollars; are you going to sit here and

tell me they were simply dealt a bum hand and that they and their families will now suffer for generations as a result with zero assistance or recognition.

Which brings me to my final point, acknowledgment. Stop making decisions to shield information from the public for fear of vaccine hesitancy. Manipulated data and censored information is not informed consent; it's deception. Shielding COVID and vaccine data from the public is borderline criminal behavior. Start by educating physicians on the actual data and what to look for so they can effectively treat their patients. I realize this is a complex issue to tackle with an endless amount of entry points, but please do not let this be a reason for inaction.

When your house is burning you don't start worrying about how other homeowners are going to feel about seeing another house on fire and then pontificate on the best PR strategy to combat misinformation around home fires. You roll up your sleeves and you pick up a goddamn hose. Please act fast, millions of lives are

counting on you. Thank you.

**DR. PRABHAKARA ATREYA:** Thank you. The next speaker is Daniela Clark. Ms. Clark.

**MS. DANIELA CLARK:** Hello, my name is Daniela Clark. I have no relevant conflict of interest to declare. I'm a 45-year-old wife and mother of two daughters. I was healthy and active before getting the Pfizer vaccine. I received my first shot on August 11th. I only felt an achy arm that night, no other symptoms. I received the second Pfizer vaccine on September 1st. That night, my arm felt achy, and I noticed the same achy feeling in my spine.

I went to sleep and woke up the next day with wrist pains, later that week they progressed to arm muscle pains. Then about a week later the neurological symptoms started. One day I scratched my face, but it felt like my hands weren't getting the full message from my brain. As if they were only receiving about 60 to 70 percent of the command. It was like a numbness.

My hands continue feeling this way. My symptoms then progressed to weakness in my legs, severe

sensitivity to sound. Tinnitus, tremors, twitches, insomnia, brain fog, head fullness, and burning neuropathy. My life went from wonderful to horrific because of the vaccine.

Simple things like eating dinner with my family became difficult. The noise sensitivity was so intense that I could no longer sit with them. The sound of people talking and of their forks touching their plates was too much for me to bear. Everything that made me happy was taken from me. I couldn't go to my daughters' sporting events. I couldn't go to dinner with friends. I could barely leave my house. I felt so sick I was constantly throwing up. I ended up losing 20 pounds.

Another symptom that I experience every single day is burning neuropathy. It feels as if someone rubbed sandpaper on my skin. Other parts feel hot, like a sunburn. I also now have tinnitus. It's something that I hear all the time, it never stops. It's like a buzzing alarm constantly going off in my head. The weakness in my legs has consistently gotten

worse. It's scary for me to think about what my future may be.

I went from a normal healthy life to a life of chronic pain and uncertainty because of the vaccine. I have seen the best doctors located in my area. They all agree that the vaccine has caused a neurological inflammatory response, but they have no idea or direction on how to help me. The FDA tells them that the vaccine is safe and effective. They don't know that it can cause small fibre neuropathy or any of the neurological symptoms that I'm experiencing.

They need to hear it from you. They need to know that the vaccine can cause chronic neurological symptoms. We need research, we need the government to fund research to help us find treatments. Doctors need studies that they can reference when treating us. Adverse reactions to the vaccines are happening. We need you to acknowledge our adverse reactions. We need research, we need treatment options. Please help us.

**DR. PRABHAKARA ATREYA:** Okay, thank you. The last speaker for this section is Ms. Pamela Warren.

**MS. PAMELA WARREN:** Good afternoon, my name is Pam Warren, 48 years old. I have no conflicts of interest. I was vaccinated on January 8th, 2021, and again February 8th, 2021. Both times, Moderna. At the time, I worked at the American Red Cross running apheresis machine collecting life-saving blood for blood banks. This required starting IVs with precision over and over during my shift.

As a healthcare worker, I was eager to get vaccinated to protect myself and the people I worked with. I got vaccinated early without any hesitation. I believed that these vaccines were safe and effective as promised. I trusted the system. Things didn't go as planned. A host of complications followed until eventually, I was unable to start IVs due to severe tremors and involuntary movements in my arm and a long list of other side effects.

I had one patient ask if I had suddenly got Parkinson's disease since the last time I saw her four months prior. I had to quit my job. I was no longer effective because I lost my steady hand and other

complications with my health were contributing to severe brain fog. I posed a risk to people I served. I was making mistakes that could hurt or kill a donor or a blood recipient.

For several months, I could not care for my children or myself. For eight months, I was too weak and sick to make one family meal, something I did easily -- with ease -- before the vaccine. My husband took care of all aspects of our home life. He is the COO of 40 primary care providers, MDs who are our friends, and even they didn't know how to help me. Their hands were tied.

Healthcare practitioners were unaware of the possibility of my rare side effects, and I was left to cope alone. I was suffering without recognition, acknowledgment, or answers, getting weaker and sicker -- 45 pounds in only a few months and still no answers or help. It took six months and nine doctors to get an urethra (inaudible) diagnosis. My life will never be the same.

I stumbled upon communities for injured people

who are forming support groups. These groups helped me find direction to healthcare providers that were pioneering a path for the injured. The vaccine injured began to take care of each other. Collecting data, explaining what types of specialists could maybe help. Why did it become the injured's responsibility to do this? The food and drug administration is responsible for protecting the public. It's time for this to happen. We, the injured, should no longer carry this burden. It is in the FDA's very mission statement to protect us.

We need this to happen now. People are suffering with no end in sight. We need your influence and expertise. Thank you.

**DR. PRABHAKARA ATREYA:** Thank you. And this concludes the open public hearing session for today. Thank you. And then Dr. Monto, could you start the next session, please?

**DR. ARNOLD MONTO:** Thank you, Prabha. We now move back onto the published agenda. We next hear from Dr. Jerry Weir, who will give us the proposed framework

for addressing future COVID-19 outbreaks. Dr. Weir.

## PROPOSED FRAMEWORK FOR ADDRESSING FUTURE COVID-19 VACCINE STRAIN COMPOSITION

**DR. JERRY WEIR:** Thank you. This is the last of the presentations, and I hope that it will serve as an entryway into our discussion topics. I'll start here. Okay, so as an introduction -- brief introduction. The FDA and its public health partners will need to make decisions regarding updating the composition of COVID-19 vaccines in the U.S. and the potential use of additional booster doses.

The Committee will be asked to discuss the process that would be used to update the composition of COVID-19 vaccines in the U.S. in consideration for use of additional booster doses. The discussion following this talk will focus on when should such decisions be made and how such decisions should be made. In other words, what are the criteria?

I'll remind you of what was stated at the very

start of the meeting a few hours ago. Today's discussion is not intended to make specific recommendations for vaccine composition or the use of additional booster doses, but it is to get the conversation started. One quick slide of background, currently authorized and licensed COVID-19 vaccines are based on SARS-CoV-2 virus that circulated in the pandemic. Virus evolution was apparent within months after the beginning of the pandemic and has resulted in the emergence of SARS-CoV-2 variants, some of which have become locally dominant such as beta in South Africa, or even globally such as Delta and Omicron.

Some of these variants have been more infectious, transmissible, and/or virulent compared to the earlier virus strains, and antigenic differences between certain variants and earlier virus strains have resulted in at least partial escape from natural or vaccine-elicited immunity.

As a result of this, composition of current COVID-19 vaccines may need to be updated to maintain vaccine effectiveness against clinically relevant

variants. The annual influenza vaccine strain selection process may provide some insights on how to consider updating the composition of COVID-19 vaccines. We touched on this a few minutes ago, but I want to spend the next three slides going through this in a little bit of detail to highlight some the key points as they might relate to compositions of COVID vaccines.

Okay, the first of the three slides for the review of the influenza vaccine strain selection process. Each year any of the previous four influenza virus vaccine strains may be replaced with a new strain. These strain changes are necessary to maintain vaccine effectiveness against predominant circulating wild-type strains of influenza virus. As you heard earlier from Kanta Subbarao, the WHO global influenza surveillance continuously monitors evolution and spread of influenza virus strains, and twice a year the WHO convenes an invitation-only consultation of experts to review and analyze data and make recommendations for the composition of the influenza virus vaccines for the Northern and Southern Hemispheres respectively.

The same questions get asked at each one of these composition meetings, and these are relevant to COVID-19 vaccines, too. Are new, and in the case of influenza, drifted or shifted influenza strains circulating? Are these new viruses spreading in people, do the current vaccines provide protection against new circulating strains of virus, and can new vaccines with well-matched antigens be manufactured in a timely manner?

Slide number two in this group. The WHO consultation reviews and analyzes data on global epidemiology and the genetic and antigenic characteristics circulating seasonal influenza viruses. Following the review and analysis, the WHO consultation makes recommendations for the composition of the influenza virus vaccines. The February consultation makes recommendations for this, the next Northern Hemisphere influenza season and the vaccine is available in about five to six months.

The September consultation makes recommendations for the subsequent Southern Hemisphere

influenza season and vaccine is usually available in about three to four months. As always, the WHO notes the national or regional authorities approve the composition and formulation of vaccines used in each country. To do that, the FDA then convenes its Vaccines and Related Biological Products Advisory Committee, or VRBPAC.

This committee, approximately one week after each WHO consultation to make recommendations for the composition of influenza vaccines in the U.S. At that composition meeting of VRBPAC, the committee hears presentations on virus surveillance in the U.S. as well as global surveillance effectiveness data for the most recent vaccines, and the availability of key vaccine reagents, and comments from manufacturers on the practical aspects of changing vaccine composition. Following review and discussion, the VRBPAC votes on the strains to be included in the influenza virus vaccines for the U.S.

After that, manufacturers submit a supplement to their license to incorporate the latest vaccine

composition recommendation and following FDA approval the manufactures distribute updated vaccine in time for the upcoming influenza season. So that is, in a nutshell, what happens with influenza selection.

So, why does this process usually work? Well, you've heard some of this already today, but the predictable seasonality of influenza. Another reason is that most influenza vaccines are of similar platforms. Even today, most of our vaccines are egg-based, but regardless of the platform, the timelines necessary for updating vaccines are fairly similar for all manufacturers. The virus genetic and antigenic data used for decision-making are generated by the WHO collaborating centers, the essential regulatory labs, and other WHO reference laboratories.

I'm not going to talk much more about this, but it is something to keep in mind that the source of the data that's used to make that strain selection decision. Another reason the process usually works is animal sera and in-vitro data reliably distinguish antigenically different viruses. These antigenic

differences among viruses generally predict differences in immunogenicity and the corresponding clinical response to vaccines. Because of the predictive power of the in-vitro antigenic data, as well as extensive manufacturing experience, new clinical data not required for an updated influenza vaccine.

And this is definitely something to keep in mind as we talk about COVID-19 vaccines. There are some times when the influenza updating process does not work well. Estimates for vaccine effectiveness for influenza vaccines are only approximately 60 percent in the overall population even when the vaccine is well matched to circulating viruses. But the effectiveness is substantially reduced, especially on highly susceptible populations. For example, the elderly when there is a poor match.

Vaccines that are less well-matched circulating influenza viruses can result for different reasons. I've highlighted two of which are also maybe applicable when we consider maybe changing COVID-19 vaccines. One of the most notable is, of course,

antigenically distinct viruses may emerge after the recommendations have been made and these viruses could co-circulate or even dominate over the recommended vaccine strains.

Everyone remembers the 2009 H1N1 pandemic virus. This emerged in the spring following the normal seasonal recommendation in the preceding February. But even more recently, their examples such as in 2014 of the H3N2 drift variant. At the time of the composition meeting, this particular virus -- there were only about one percent of all virus isolates were of this type, but by September two-thirds of all virus isolates were this type. So, this is an example of something that existed but then became dominant over the course of the following month.

There are also manufacturing issues, and sometimes these cannot be resolved in a timely manner in these preclude production of a well-matched vaccine. It's well known for influenza vaccines that their effects due to egg adaptations -- amino acid changes that are due to egg adaptations. But sometimes there

are difficulties in deriving high growth candidate vaccine viruses.

Now both of these examples are probably unique to influenza virus vaccines, but what I wanted to do was highlight the point that manufacturing issues are always something that have to be considered when one makes any change to a vaccine. For influenza, there are some contingency plans that are available in situations of severe mismatch. And there have been examples of supplemental vaccines that have been made.

Usually, this means that both the WHO as well as the national regulatory authorities like the FDA convene and make a decision to make supplemental vaccines. The 2009 pandemic model valent vaccine was one of these, but there were other examples as far back as 1986 when the supplemental vaccines were made.

Now, clearly, this is an example of framework that one could consider for how one might make changes to COVID-19 vaccines, but there are obvious challenges to adapting such a model. The influenza model to COVID-19 strain composition decisions, and I think I

have several slides that just list some of these. Some of these may have already been mentioned earlier in the day, but we'll go through them again just so that we're aware of all the things that one needs to keep in mind.

SARS-CoV-2 variants have not appeared in a predictable seasonal pattern, at least not yet, and they have not always spread globally. Nevertheless, as you saw in some earlier presentations, there have been substantial ways of -- a virus weighs each of the past two winters. They're also, unlike influenza, they're actually more types of vaccines being developed and produced for COVID-19. These multiple vaccines are either in development authorized or license -- and as you've heard in a couple of different talks -- several manufacturers are evaluating vaccines with updated compositions.

These include variant specific model valent vaccines as well as some multivalent combinations, and these clinical trials are ongoing and in various stages of progress. We hope that some data from these trials will become available over the next few months. It's

important to note that the development of modified COVID-19 vaccines by the different manufacturers, these trials are not being currently coordinated with a respect to string composition being evaluated. I think Dr. Johnson touched on this during his talk. And also I think he touched on the fact that time needed to manufacture an updated COVID-19 made different significantly depending on the vaccine platform, as well as the things like the manufacturers' experience as well as manufacturing capacity.

Some more challenges to adapt in the influenza model. Because of limited experience to date, FDA currently requires vaccine-specific clinical safety and effectiveness, immunogenicity, data to support authorization of a modified COVID-19 vaccine from any given manufacturer. This clearly adds to the time involved in updating a COVID-19 vaccine.

There has been a recent update to our guidance for industry of emergency use authorization for vaccines to prevent COVID-19 -- this is in appendix two -- evaluation of vaccines to address emerging SARS-CoV-

2 variants. This guidance is applicable to strain change modifications of authorized or approved COVID-19 vaccines -- often called prototype vaccine -- expressing SARS-CoV-2 S-protein.

It refers, in general, to vaccines of the same platform and manufacturing process for both prototype and modified vaccines, and the guidance only covers valent modified vaccines but some of these recommendations could be adapted for evaluation of multivalent vaccines.

Modified vaccines are recommended to be evaluated as a primary series and as a booster dose. Evidence for effectiveness of these modified vaccines will be derived from immunogenicity data, neutralizing antibody against clinically relevant variants, and demonstrated effectiveness -- and with demonstrated effectiveness of the prototype vaccines. All of this assumes neutralizing antibody to S as a major component of the vaccine protective response.

And I think this is the third slide of some of the challenges. Ideally, the process of changing the

COVID-19 vaccine would be coordinated globally, you heard from the WHO presentation a couple of hours ago. Nevertheless, global coordination may be challenging due to a lot of factors. One, is of course the unpredictable nature of SARS-CoV-2 evolution. As well as regional differences in variants of concern, circulation or dominance. There are also different regional levels of vaccination coverage and type of vaccines that are in use in different parts of the world.

And, as I've already mentioned in one of the previous slides, there is a variable timeline for the availability of the clinical data for different vaccines that might support the need for a modified vaccine.

In other words, taken together implementing and coordinating a global process will likely take some time. And I remind you that the influenza global coordinated process has been a process for years and really decades and it does take time to get all of this into place. I think for us, we think that a process

for updating the composition of COVID-19 vaccines in the U.S. will need to be flexible as well as orderly, transparent, and data-driven. And we'd like the committee to consider -- give some consideration to scheduling a periodic review of COVID-19 epidemiology and the available clinical data for vaccines against variants of concern.

This slide lists some of the basic conditions that would be necessary to make any recommendation for changing a COVID-19 vaccine composition. First of all, the epidemiology data need to identify an antigenically distinct variant or variants that are likely -- that either are or will likely become dominant. There needs to be immunogenicity and effectiveness data that indicates that current COVID-19 vaccines provide insufficient protection against circulating variant viruses. And then there needs to be data to justify such a recommendation for changing the composition, and that needs to be available from at last one, and ideally more than one, COVID-19 vaccine.

In other words, we need clinical data to help

us make a recommendation for a change, as well as each manufacturer that would implement that change would have to supply -- and this is the fourth bullet -- their own clinical data to support the safety and effectiveness of their modified vaccine. And, of course, any one of the very basic conditions is that vaccine manufacturers will have to be able to manufacture and deliver a modified vaccine in sufficient quantities and in a sufficient timeline to make an impact.

I think I have two slides now to show, once again, the complexity of this. Some additional questions that would need to be considered in any strain composition decision. And these are some questions. Does the available clinical data support changing the strain composition of vaccines currently in use? Should modified vaccines be monovalent or multivalent? What strain should be included? Does the available clinical data indicate how well a modified vaccine would impact breadth of coverage against circulating and potentially emergent viruses?

The breadth of coverage considerations different for vaccines used as primary series or booster series or booster doses. Some more questions. How often should the composition of COVID-19 vaccines be reviewed for a possible composition update? Should this be something like yearly, like for influenza, or should be as variants of concern appear and become dominant? Are there and what should be any contingency plans that we should consider in case a novel SARS-CoV-2 virus emerges and is not covered by available vaccines?

If the strain composition is recommended, how is a smooth transition to a use of a modified vaccine implemented? And by saying this, I remind you that recommendations for seasonal influenza vaccines apply to all influenza vaccines and those vaccines have a dating period that eliminates any possible confusion among the different recommended vaccines.

And finally, this is probably a little too much to get into today, but it's worth keeping in mind, and that is what additional data or experience could

expedite the process for COVID-19 vaccine composition changes by limiting or obviating the need for clinical data? Which, I've already told you is something we would still insist on, at least at present time.

So, this slide presents a framework. I remind you before I even read it that the framework is tentative, it is thrown out to be a placeholder to spur the discussion that's hopefully going to follow, and nothing is etched in stone. We would presume that we would meet again, talk to this with the VRBPAC, but we would like to get the conversation started.

But we start with assuming that the FDA would seek the advice of the VRBPAC to make recommendations for any change in composition of an authorized or approved COVID-19 vaccine in the U.S. We suggest that on some routine basis -- and this is one of the topics for the committee to talk about -- that on this routine basis the FDA and VRBPAC would review the epidemiology that's circulating in SARS-CoV-2 variants in the U.S., the effectiveness of available vaccines in use, the available clinical data and manufacturing concerns for

modified vaccines in order to determine whether to recommend an updated vaccine for use in the U.S.

We also suggest that there should be some thought given to a collaborative plan -- this is going forward -- that includes manufacturers, the FDA, and other public health agencies to develop such a plan that would provide the necessary clinical data needed for the future vaccine composition decisions.

And then, any effort to make contingency plans would be a good idea. These plans should be developed to respond to any emerging variant that escapes protection provided by currently available vaccines. On the other hand, if the WHO makes such a recommendation, the FDA and the VRBPAC would almost certainly evaluate whether that recommendation should be implemented for the U.S. with consideration given to pretty much the same thing that I list at the top of the slide.

The epidemiology of circulating SARS-CoV-2 variants in the U.S. The capability of manufacturers of authorized vaccines to implement such a

recommendation in a timely fashion, and of course, as I've already mentioned for each manufacturer, the availability of clinical data to support the safety and effectiveness of their vaccine.

And my last slide is considerations for use of additional booster doses. A recommendation for additional booster dose might follow a recommendation for changing a COVID-19 vaccine strain composition that occurs either as a result of a scheduled or an ad hoc review of COVID-19 epidemiology and vaccine effectiveness. Even if the available data continue to support the use of a prototype vaccine going forward, the periodic use of additional booster doses, for example, annually similar flu is one example -- these booster doses may still be needed to maintain adequate immunity.

Any recommendations for the use and the timing of additional booster doses should consider the goals of the vaccination program, for example, preventing morbidity and mortality as opposed to mild disease, infection transmission, should consider which

populations the additional booster doses are warranted, as well as practical and operational aspects of public health vaccination.

So that's the end of the talk. The topics for discussion are the same ones that Dr. Fink provided at the very start of the meeting. Maybe I won't read these now since we'll go back into them in a few minutes. But I'll remind you again, they're not voting questions. We know they're complex, we know they're difficult, but we would appreciate any input, any suggestions that the committee have -- like I said -- in order to get this conversation started rather than wait until the next crisis to start talking about it. So, I'll stop there.

**DR. ARNOLD MONTO:** Well, thank you, Dr. Weir. You've given us a lot to think about.

**COMMITTEE DISCUSSION OF QUESTIONS**

**DR. ARNOLD MONTO:** Well, thank you, Dr. Weir. You've given us a lot to think about. And, what I propose is that we start out with a discussion focusing

on your presentation, before we go into a more general discussion looking at the specific questions that we have been asked to answer. And I'll start out by focusing, which is my biggest worry, on the timeline the doc- (audio skip) --

**DR. JERRY WEIR:** I think I lost your sound.

**DR. PRABHAKARA ATREYA:** Dr. Monto, we can't hear you.

**MR. MICHAEL KAWCZYNSKI:** There we are, Dr. Monto, we got you. Okay, go ahead.

**DR. ARNOLD MONTO:** Okay. All right. You hear me now?

**MR. MICHAEL KAWCZYNSKI:** Yes, we hear you now.

**DR. ARNOLD MONTO:** What I was saying is that my concern is the relatively short timeline we have in order to develop some (audio skip) clinical data. And the date that we heard from Dr. Johnson, which was in May, in order to be able to have things started and available, doesn't that really (audio skip) --

**DR. JERRY WEIR:** And, once again lost you.

**MR. MICHAEL KAWCZYNSKI:** Dr. Monto? He's

connected but he's having -- he's on his cell and I bet you he's just dropping for a second there. So let's just give him a moment.

**DR. PETER MARKS:** This is Peter Marks. I think Dr. Monto is trying to say that there is a very compressed timeframe to be able to make a decision regarding the booster composition. Based on what was presented by Dr. Johnson. So I think that's probably what he was --

**DR. ARNOLD MONTO:** That's exactly it, and I'm worrying about the need for clinical trial data because the clinical trial data has to come from existing variants. You can't do a clinical trial on a variant that's going to emerge.

**DR. PETER MARKS:** Right. I'll also tell you that in conversation, just for the committee's information, that probably we should be thinking of a May to June timeframe here. There is probably some wiggle room, but just not that kind of a lot more time, but it's a little bit more time.

**DR. JERRY WEIR:** Yes, and so we do think that

we're going to have some clinical data from some manufacturers over the next couple of months. But, back to what you just said, Dr. Monto. Even some data on variants that may not be under consideration, may help us understand how, for example, a bivalent vaccine may work. So there are some things that we can learn from whatever clinical information we can look at.

**DR. ARNOLD MONTO:** Okay, let's go on the list. Dr. Meissner. And, next will be Dr. Bernstein. I was asked to warn people in advance before they're called. Dr. Meissner.

**DR. CODY MEISSNER:** Thank you, Dr. Monto, and Dr. Weir, such a provocative presentation. And the problems are substantial. But it seems to me that one of the first issues that need to be thought about is listed in your slide number 12 that is the second bullet. And it says, immunogenicity and effectiveness data indicate that current vaccines provide insufficient protection against the circulating variant strengths.

And so the question is going to be, what is

insufficient protection? I mean, since we don't know the correlates of immunity we're going to be so dependent on hospitalization rates, death rates. And that's where it will be so important for the CDC to be able to give us accurate figures about hospitalizations with COVID and hospitalization because of. But at what threshold will we say, gee, you know, the current vaccine is cross-protection but it's not adequate?

**DR. JERRY WEIR:** Yeah, obviously, that's a judgement call and it's a tough question to answer. Although we put in immunogenicity, we clearly wanted to stress that effectiveness data is part of that consideration. Again, this is not like influenza, where one can look at in vitro data and actually make that prediction that a difference in immunogenicity of eight-fold in a HI assay really translates to a decrease clinical benefit. So, yes, I do think it needs to be defined, but I think the effectiveness of current vaccines will be a key driver in determining when that threshold, whatever it is, is reached. I don't know if Dr. Fink or Dr. Marks wants to elaborate

on that, but, yes, it is a key question.

**DR. CODY MEISSNER:** Because I remember when this question was asked of Pfizer, why they didn't work off the Delta strain, and why did they continue to use the Wuhan strain, the D614G mutated Wuhan strain. In answer they put up a slide and showed that it induced pretty good serologic protection against a variety of mutants. And, you know, that was probable accurate. So, at what point will we say the vaccine isn't working well enough?

**DR. JERRY WEIR:** Again, I think it's a tough question. I think effectiveness data is probably going to be one of the key drivers, because I'm not sure that we can easily at this point in time point to a particular drop in immunogenicity that we know translates to that effectiveness data. Hopefully over time we will get something like that, but I don't think we can right now.

**DR. CODY MEISSNER:** Thank you.

**DR. ARNOLD MONTO:** Let's move on. And I will interject, Dr. Weir, that sometimes with influenza we

get into debates about whether small changes do or do not result in significant drops in efficacy and this here is a case in point. So, it's a mixed blessing with having a pseudo correlate of protection with influenza. Dr. Berger, I see the next hand is yours. Dr. Berger?

**DR. ADAM BERGER:** Thanks. I'd like to actually just follow up on what Dr. Meissner was just talking about, which is, what is the real efficacy we're looking for here? And, I think your slide and I'll point it on Slide 16, which is, what's the goal of vaccination program? Is it to reduce (audio skip)? Is it to prevent (audio skip) disease? Is it to prevent pertinent severe disease?

And I think what we need to be cautious about is making sure whatever we're indicating is the efficacy here, that there is actually causality. I think what we've seen so far, at least from the data that we got today, is that even though prevention of infection seem to be waning, it isn't seemingly having a significant drop in the efficacy from severe disease

of hospitalization or death.

And, so, I want to make sure that when we're thinking of that, that the framework takes into account the outcome that we're trying to achieve. Because we could go down a bit of a rabbit hole and make changes to a vaccine that maybe prevents infection but doesn't actually alters the end result. So, what is it that we're trying to get is a really important question for us.

If I could, I'd also like to just question -- or at least put out there. Manufacturing capacity itself, it would be great to be able to hear directly from the manufacturers as to what their capacity might be. I think some of the points were made earlier that who have potential for these new MRNA vaccines to help develop that process a lot faster. It would be great to be able to hear directly what kind of capacity they might have. To for instance, continue the development of an existing prototype vaccine while at the same time being able to ramp up and scale for production of possible mutant variants for development or even if by

valent at the same time that data's being collected. So, it would be really good just to get an understanding of that.

The last point I'll make, and I promise I won't go on much more, is just that the timing itself seem to be based on that seasonality coming up and trying to make sure that we're hitting at the same type of timeline that we hit for flu vaccination rate. And I'm not sure that right now the data support seasonality for COVID-19 too. It might actually be on a different timeline. I recognize that there are those implementation questions about do we go ahead and try to suggest that this would be given at the same time you would give a flu vaccine or are we asking the public to come in for a second shot -- is a huge one. But I think it's just that question for the timing of when we would actually need to make decisions may not necessarily be tied to the same timeline that flu is.

**DR. JERRY WEIR:** Thank you for all of those points. I would agree with all of them. They mention, once again, some of the difficulties. I would make one

suggestion, though, that back to hearing directly from the manufacturers. That is something that would be good and maybe if we meet again within a few months with some clinical data that at that time when the manufacturers present some of that data, we also get them to tell us what is realistic and practical for their particular vaccine. So, maybe we can do that all at the same time.

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

**DR. JAMES HILDRETH:** I just want to follow up on a point that Dr. Meissner made earlier, which is that about immune correlates. I brought this up in a very first meeting that if we could determine an immune correlate for these vaccines, it might expedite the issue of identifying those that are going to be successful and protective. Because it's going to be a limited time to do this, given Dr. Bedford's presentation and the population dynamic for this virus, having an immune correlate that we could look to or define and the serum of the vaccine recipient or volunteers in trials will help us a great deal.

Is there any effort being made to focus in on immune correlates, cytotoxic T-cells, (inaudible) T-cells, something other than antibodies?

**DR. JERRY WEIR:** Yes. There's clearly a lot of effort; I'm not sure I can give you the current status on it. But there's definitely a lot of effort. I couldn't agree with you more that that would make life a lot simpler. And that I, like again, I'm a very strong supporter of that. I think the more we can understand that, the closer we can get to understanding a correlate, all of our lives would be a lot easier. And, yes, I'm sure there's a lot of effort going into it.

**DR. JAMES HILDRETH:** Okay. Thank you.

**DR. ARNOLD MONTO:** Now, Dr. Bernstein.

**DR. HENRY BERNSTEIN:** Thank you. Such challenging questions that you raise. And I do think it's important, as you mentioned, the challenges to be transparent and data-driven and the need for clinical safety and effectiveness data to support authorization.

Picking up on what my colleagues were saying

before. You anticipate conceptualizing vaccine effectiveness a priori and coming up with a minimal acceptable estimate for the different outcomes that Dr. Link-Gelles presented, a different estimate for infection versus ED/urgent care versus hospitalization and death?

**DR. JERRY WEIR:** It sounds like a good idea to me, but somebody else such as Dr. Fink or Dr. Marks may be better able to answer that.

**DR. ARNOLD MONTO:** Yeah, this brings up a point. Should -- Jerry, do you want to be on the firing line for this, or should this be a group response? And, Dr. Fink, could you tell us, would you like to be part of the firing line?

**DR. DORAN FINK:** I'm willing to help answer questions, certainly. And, with the caveat that I feel the pain of the committee; there are no easy answers here. Just to respond to Dr. Bernstein's question. I think we're talking about maybe two separate things. First of all there's the question of whether currently available vaccines are providing adequate protection.

That's what Dr. Meissner brought up. And how do we know whether currently available vaccines are providing adequate protection.

And there Dr. Weir answered we're going to be relying heavily, mainly on vaccine effectiveness estimates, some studies such as the CDC has presented earlier today. And we will need to ultimately decide what threshold level is that we would consider to be acceptable versus unacceptable. And I wish I had a suggestion now, but I don't. And I would be interested to hear the thoughts of the committee on this; on what this sort of threshold might be.

And then there's the question of if we determine that a strain change composition is needed, how do we assess the safety and effectiveness of modified vaccines that are based on a prototype vaccine manufactured using the same platform?

And there Dr. Weir presented a slide that referenced our UA guidance and specifically an appendix in that guidance where we lay out the considerations -- and actually, at this time, the requirements -- for

clinical evaluation of modified vaccines, looking at safety and looking at immunogenicity. These are not large studies but they are designed to provide what we think is the essential minimal information that one would need to really feel comfortable deploying a modified vaccine.

And, in terms of the immunogenicity data, if you look into the details of that guidance and that appendix, we requested a variety of immunogenicity analyses using a variety of input viruses and neutralizing antibody assays to assess the breadth and magnitude of the immune response elicited by the modified vaccine, in comparison to the prototype vaccine.

And it would be based on the totality of data looking at those immunogenicity analyses in aggregate that we would have to make a decision as to whether there is a compelling reason, based on those immunogenicity data, to conclude that the modified vaccine would have an advantage over the prototype.

**DR. HENRY BERNSTEIN:** Thank you. Not easy to

answer.

**DR. ARNOLD MONTO:** Okay, let's go on to Dr. Gans.

**DR. HAYLEY ALTMAN-GANS:** Thank you very much. I really appreciate the ability to have this conversation about what it may take actually to understand and control this pandemic moving forward. I think one of the really obvious things that have come up, and it hasn't been stated explicitly, so I think that it's actually important to state, is that we're using things like influenza or other respiratory viruses, which are fairly settled and actually we have a huge amount of information.

And obviously what we're all grappling with is that this is an unsettled environment in which we're trying to move forward. And while it's helpful to use some of these other platforms, obviously there have been the obvious differences that have been pointed out. And I think what's really important, and I appreciate Dr. Weir, you saying like I think that we actually have to come together with some of the

information that we've been asking for today, in a very routine and systematic way moving forward, until this is settled science. And that we actually can move to a less frequent meeting of the minds.

And I think a couple of things that people have really talked about but what I think the committee needs to hear in order to actually make some of the recommendations that has been asked of us and will be a voting later on at some later point, are all these ideas of correlates of protection. While everyone's saying there are studies out there or things are happening, I think there actually has to be explicit information that this committee needs.

And it sounds like this committee needs really more than neutralizing antibodies. We have some correlates that people feel comfortable in influenza, but actually several of us have actually even asked for some of these other correlates for the influenza information to make better decisions.

Anyway, so obviously T-cells are important. And I think what people have fallen back on is really

trying to do complicated T-cell studies. And there have been several labs that have done things like iCRA (phonetic), for instances, that actually are helpful and could actually move people forward potentially in an easier way. And actually have them more commercially available. The other thing is mucosal immunity.

The other parts of it, and we've heard clearly from the public and for individuals who would like to hear more about the safety data. And so I think, while it's been sort of, again, spoken about but not explicitly stated, that we would need actually the ongoing safety data. So we've put these very elaborate systems, we have the VSV. We have the Prism. We have lots of reporting data. We're not actually seeing that being updated to the committee, and we would need those to come along with it.

And the last we would need, obviously, also, updates on what platforms are coming forward. Because in order to make decision about what it is that we're being asked, which is current, we also need to know what

is actually in the pipeline, which we don't hear about on a routine basis as well.

And, so, those are some of the points that I think would need to happen and as you suggest, Dr. Weir, on some, particular cadence that we would all need to come together with that information.

**DR. JERRY WEIR:** Thank you a lot; it's very helpful.

**DR. ARNOLD MONTO:** Yes, and I agree that we have insufficient information right now to give you in any way precise comments on all of the discussion questions. I had hoped that we would hear more about some of the trials that are in the pipeline, clinical trial, because this might help us in going forward. And there are a lot of other things that we would need.

We would also need a little more of a strawman to discuss, something that you would propose, which you almost did in one of your slides. Rather than more of these open questions, such as, how often should the adequacy of strain composition for available vaccines be assessed? The answer to that is as many as you can,

as often as you can. So it's rather difficult to try to opine about some of these points without additional information. And, as I was saying (audio skip) proposals, even though -- at least for discussion. Having said that let me call on Dr. Rubin.

**DR. ERIC RUBIN:** I'm afraid I'm going to agree largely but in part with Dr. Gans, but we can save that for later. What I wanted to ask you about Dr. Weir is specifically about the surveillance data that in your slide set it said surveillance data for the U.S. But in fact, when these viruses come to the U.S. it's really too late. They spread rather quickly and that certainly was the case with Omicron and with Delta. But there was a lot of early waring in other countries. So, I guess I would urge us to be considering those data as well.

**DR. JERRY WEIR:** Yeah, I think what I was trying to get across, though, is that if this committee was presented with a recommendation, for example, from WHO, I think we would have to ask ourselves what the situation was in the United States. And that being, although you're right that sometimes different variants

have spread globally, there's a couple of examples of the Beta and the Gamma that did not. And, so, I think we would have to evaluate the U.S. as well as the larger picture. And that doesn't mean it's an easy call, but we would have to look at it like that. We'd at least have to look at our regional as well as the global situation. I think that's what I was trying to get across.

**DR. ARNOLD MONTO:** Dr. Offit.

**DR. PAUL OFFIT:** Yes, thank you. I guess what I'm struggling with a little bit is use of the term "booster." I agree with Dr. Berger's and Dr. Meissner that a reasonable goal for this vaccine is protection against serious illness. I mean this is a mucosal virus, you know, like all mucosal viruses. Whereas natural infection immunization can protect against serious disease, it's not going to be very good at protecting against mild diseases because neutralized antibodies will last for several months but usually be well down after six months, which is what we're seeing here.

So, the good news is that at least to date, for all the variants that we've seen, it looks like the protection against serious illness is holding up. And that is consistent with studies by people like John Wherry and Shane Crotty, showing that you still have high frequently of memory B cells, memory T cells, six months, eight months, nine months later. So that's good.

But I think the decision we have to make, it seems to me, is when do we no longer see protection against serious illness because a new variant has arisen? And if that's true, is the word really "booster"? Because, really, what are you boosting? Usually when you boost, when you give a dose of vaccine you're boosting neutralized antibodies.

I would argue that if you, having variant that is so distinct in terms of epitopes recognized by memory B or T-cells, that you're no longer getting protection against severe disease. Maybe what you're talking about then is a primary series. I mean, you alluded to that, Jerry, in one of your slides. And I think that's going

to be part of this.

I mean, this virus isn't flu. You get a flu vaccine every year in large part because even if you're immunized or naturally infected the year before, you may not be protected against severe disease the next year. To date, protection against severe disease does seem to be holding up so I guess I don't see it in exactly the same way that I do the flu model where you need a yearly vaccine. Those are just my thoughts. I'll be curious to hear yours.

**DR. JERRY WEIR:** Well, I think, you're right, I mean, there's so much we don't know. But I think there is a worry that protection against severe illness won't hold up forever. And that, therefore, one may need to do -- you can call it booster, you can call it annual vaccination, you can call it some periodic vaccination. At some point that becomes semantics as much as anything else. But I think that is still the worry is that the drop in protection against some outcomes may portend the drop in protection against the more severe ones that you refer to. Again, there's just an awful lot we don't

know. But I think that's the worry.

**DR. PAUL OFFIT:** I think the key player here, and maybe Amanda Cohn can comment on this, is the CDC. I mean, we need to have rapid access to protection data, especially against severe disease, and that's where the CDC can really help us. So, thank you.

**DR. JERRY WEIR:** Can I make one quick comment, both for you and back to Dr. Monto? I mean, if we come back to this committee and talk about this again, of course we would bring in the CDC. We would bring in all sorts of experts. And we would cover everything we could before we would -- and we would throw out a strawman for you to consider. So I think we would do all of that in any sort of subsequent meeting.

**DR. ARNOLD MONTO:** Dr. Marks, where do you want us to go at this point? Because you can see that this is a very broad discussion, not really focusing on some of the questions that you would like us to answer. And I really need some guidance about what would be helpful to give you what you need today because we know this is going to be a protracted process. Try to come up with

some of these conclusions that will guide future thoughts about a process which really we have very little time for; it's a period of months.

**DR. PETER MARKS:** Thanks very much, Dr. Monto. I think it might be helpful to put up the slides with the questions and, perhaps, just see if anybody wants to add anything as we go through and flip through this. I think there were four in total. Would that be acceptable?

**DR. ARNOLD MONTO:** That would be very good. I think we will find that some of these points really are not independent; they relate to each other. But, I think we need instructions.

**DR. PETER MARKS:** I completely agree with you that some of these may -- but just to -- we have already touch upon some of these.

**DR. ARNOLD MONTO:** Right, and some of them really have no answers. Such as, how often should the adequacy of strain composition -- that's going to be so dependent on epidemic behavior and availability of data. I could see in the best of all possible worlds, not

having a BA.2 wave and having a quiescent summer. That would provide us with no additional data before the winter if this virus is going to be showing seasonality.

So, we really have to be very flexible in some of the conclusions we come to. But the first point is what considerations should inform strain composition decisions, to ensure that available COVID-19 vaccines continue to meet the public health needs and the role of VRBPAC and FDA. That's relatively easier, if we talk about what the role of VRBPAC and FDA are.

**DR. PETER MARKS:** Now, I think --

**DR. JERRY WEIR:** If it's easy, let's knock it off then, Arnold.

**DR. PETER MARKS:** I think that's right.

**DR. ARNOLD MONTO:** Yes, let's do that, because that's an easier one.

**DR. PETER MARKS:** So the idea here, I think, that --

**DR. ARNOLD MONTO:** Especially since some of our members would like to be opining as frequently as possible.

**DR. PETER MARKS:** Well, just to understand here, one of the points of trying to have this meeting was so that we would be able to open a dialog here about the need for what we might expect, and the role of VRBPAC and FDA in coordinating strain composition, again, with the overlay of WHO, if they come up with a recommendation, is to try to understand how you coordinate this because we have multiple manufacturers.

We are talking about some vaccines in development that might not be authorized or approved yet that could also be coming into the mix. How do we essentially unify what we're doing for a booster? Because that was, I think, one of the principles to discuss here is, is there some import into doing this unification. Because one could say, well, just have different boosters from different manufacturers. And if somebody wants to make an Omicron monovalent, and somebody else wants to make a bivalent Omicron prototype, those would be just fine.

On the other hand, I think that from a public health perspective, at least what we thinking and I

think open for the committee's input, was that given the potential confusing that could occur with that type of an approach, in terms of our mixing and matching of vaccines, it might be better to try to have a unified approach with a strain selection or a variant selection much the same as we do for influenza.

**DR. ARNOLD MONTO:** And further than that, the point was raised about calling it a "booster." And what if somebody, if we go into a scenario of vaccine available, let's say, in October, what are the different approaches for those individually who've not been vaccinated before versus those that have. We're going to go to the situation as we do with flu in young individuals who have to get two inoculations as opposed to those who would only have to have one.

But the question you have given us is, what is the role of VRBPAC and the FDA; and I think that is something which we all feel we should have a major role in. Question is exactly how and what the questions are going to be. Let's take this out to the committee. Dr. Nelson, you have your hand raised.

**DR. MICHAEL NELSON:** Well, thanks for shifting gears, Dr. Monto, to a very difficult but, perhaps, easier question with regards to the role of VRBPAC and FDA. And thank you, Dr. Weir, for providing such a structured approach. Albeit, challenging with respect to the wide open questions that are available. And I will put my foot forward proposing that we do have a unify approach to vaccination and strain content for the vaccines offered here in the U.S., pending any additional data and discussion from the rest of the committee.

I think it will be important, seeing the confusion that's already occurred with the launch of vaccines that have been approved and put out for emergency use authorization by the public, to have different constructs of vaccines available in the U.S., while adding increased complexities,

I also do want to revisit the challenges of timelines and the sincere worry that you, Dr. Monto, and I believe other members of the committee have. And, perhaps, challenge the notion, when you talk about the

role of FDA and this VRBPAC committee, in how we approach a change in vaccine construct.

And the reason I bring that up is I reviewed the timeline of the Omicron wave that we just experienced. Even if we had a perfect kaleidoscope, November 26 was the identification of the variant of concern. December 1st, or early in December, the first U.S. case was reported. That represents less than five months since designation of the VOC, and approximately three months after the first U.S. case, when we didn't even know whether that particular variant was going to hit the U.S. So to make a decision on a change in vaccination and to launch it in time to prevent that disease would not have occurred with the Omicron variant specifically.

So had we pivoted all our vaccines to that particular variant, we would be at risk of not only missing the wave, but, perhaps, being so antigenically distinct from others that will come, we may have missed the boat in providing baseline and advancement in immune protection for those variants that are to come.

So I would propose that we address or adopt a framework that is more intentional. That really looks at making changes only when we feel that it's competent and it's going to substantially lead to a longer duration of baseline immunity. There's no guarantee that every emergent variant is going to be the bases for the next variant, unless it's globally present.

So, I think that we need to use our predictive models and, perhaps, pivot to a multivalent approach that includes some baseline immunity from historically evidence-based strain, providing broad immunity against multiple variants. And then intentionally and cautiously fold in additional variants that may provide a longer range approach to sustain immunity both on the humoral and cellular side. Be interested in your comments, Dr. Weir.

**DR. ARNOLD MONTO:** Thank you for that very specific proposal, which gives us a bit of a framework to continue our discussion. Dr. Sawyer.

**DR. MARK SAWYER:** I would like to step off Dr. Nelson's comments and make a few others from sort of the

public health implementation standpoint. I think, clearly, whatever we do -- lacking clear correlates of protection information -- would make this simple as we need to continue to focus on the worst case, which is severe disease. And, we need to change strains when we're losing that battle, to be defined by future discussions.

I think the current situation where we're feeling compelled to boost every four months, potentially, is not sustainable. So to the point of composition of vaccine in the future it seems to me, from what we've heard today, that a multivalent vaccine is going to be important to hopefully prolong the duration of protection against the foreseeable variants that will emerge.

But I think overall we have to keep this as straightforward as possible, and Dr. Weir's presentation and at least one other FDA speaker raised the question about whether the composition -- if I understood the comment -- that whether the composition of the vaccine would be different for a primary vaccination versus

boosting. Which I didn't really understand, I don't see why we would go backward to a previous version of the vaccine, even if someone had not previously been immunized. So I would like to understand that a little bit more as we go forward.

And the last thing I'll say is we clearly need a unified approach to manufacturing. It would be impossible to keep track of multiple different vaccines with different compositions. So I'm in full support of VRBPAC picking the strains and having all manufacturers make a vaccine with those strains.

**DR. ARNOLD MONTO:** Dr. Marks?

**DR. PETER MARKS:** Yeah, thank you. Dr. Sawyer, thanks for raising this. I think we internally, I'll speak for Dr. Weir and Dr. Fink on this one. We had a discussion about this issue that you raise. We agree with you; we would not be going backwards. I think if you as the VRBPAC decided to recommend a strain change, or new variant composition of multivalent vaccine, that would have to become what we would use for primary series.

It would be too confusing, and potentially dangerous, to have different regiments like this, especially when you're trying to vaccinate tens of millions of people, to have a different primary composition. And I don't think it would make a lot of sense either. So, we would assume that much like with flu, once we move to a new composition for whatever we call it -- we can call it a booster. We can call it Joe. But whenever we do Joe, it will also change the composition of the primary series.

**DR. ARNOLD MONTO:** But not necessarily the number of doses.

**DR. PETER MARKS:** The number of doses, I think, that's been established, I think, as part of what we established -- we would keep the number of doses. Unless the manufacturers bring us some new data, the primary series would remain the number of doses in the primary series as a two-dose primary series. And then this would then be the additional doses that would be used wherever we deployed them. Doran, do you want to pick up from here?

**DR. DORAN FINK:** Yeah, I just wanted to add that this issue of avoiding unnecessary confusion by having a unified approach is one that really does impact the question of whether to -- if one were to proceed with extreme composition change, should it be toward a monovalent vaccine that is directed against a variant, say Omicron, or should it be a multivalent vaccine. And what I think certain people have hinted at, and some might have said more explicitly, is that pivoting towards a monovalent vaccine directed at something like Omicron runs the risk of really narrowing the breadth of coverage for people who might be getting that modified vaccine as their primary series. That would be a large concern.

And so thinking in practical terms, thinking programmatically, it really does seem, at least to me, to make a compelling case for any modified vaccine really ensuring breadth of coverage to optimally be able to handle whatever variant might come.

**DR. ARNOLD MONTO:** And, trying to move us to some kind of consensus, can we have comments from the

committee about anyone who does not feel that what we should be working towards is a multivalent which could include a bivalent vaccine, which would be uniform across platforms, whatever they may be at the time. Dr. Marks?

**DR. PETER MARKS:** I just wanted to mention that I think there's obviously the idea of a bivalent or multivalent. There's also the concept, and I think a little bit of this was presented by Dr. Beigel, that there may be other monovalent vaccines which may end up producing the antigenic diversity that could coverage much like a bivalent would. It might not be the current prototype, but it might be another. So, I think we would do it obviously in a data-driven manner, whether it's a bivalent or whether there was some data that another monovalent could provide similar type of protection. It's just open to what the data show.

**DR. ARNOLD MONTO:** Well, let's then discuss that this would be something which is data-driven, based on clinical evidence of efficacy, which is what my problem with something that has not actually circulated

even though it might be -- whether you're going to have data on efficacy by the time we have to make decisions. But, if that is possible that would certainly be part of the equation. So let's have some discussion about this in particular. I'll call on the next hand that I see raised, which is Dr. Meissner.

**DR. CODY MEISSNER:** Thank you, Dr. Monto. I think it certainly makes sense to have a common goal, but the question I have is this. When the vaccine manufacturers make the influenza vaccine, they are aware of a certain market size. And that is pretty predictable, and it will be there. So that justifies their investment in developing that vaccine.

But that may not be the case with COVID. That is, we probably wouldn't even have had as many vaccines had it not been for the support from BARDA, which funded Operation Warp Speed. And there probably won't be so much federal funding, and maybe that's not correct. Dr. Marks, you may be able to correct me there. But, will the pharmaceutical companies want to develop a new vaccine if there isn't assurance that that will become

an authorized and then recommended vaccine by the CDC? I mean, it would be a gamble for them.

**DR. ARNOLD MONTO:** Dr. Marks, would you comment on whether we should be concerned with the marketplace issues, or should we go on the theory that this is going to be taken care of?

**DR. PETER MARKS:** Great question here. I think that we probably need to be thinking here about the public health perspective, and Dr. Cohn could probably also chime in from CDC. But, I think what I alluded to at the beginning of this idea of waning immunity, combined with the fact that, remember, as presented by CDC, only half of Americans have actually received a third dose of vaccine. So they probably do not have optimal immunity, and they will not have optimal immunity going into a fall/winter season. We will probably have the increased drift of whatever we are going to see, whether it's an Omicron descendant or some other variant that could come kind of out of left field -- we've seen that already, so it could happen again, not likely but it's there -- and the seasonal

respiratory virus.

That combination makes us think that we probably have to be prepared at least from a standpoint of national security, making sure that we can protect our population, to have a vaccine in hand. And I think the manufacturers are committed to developing one. And I think Congress' funding, not quite withstanding, yet I think there's a fair amount of commitment to ensure that one is made available if it's felt to be indicated.

**DR. ARNOLD MONTO:** Thank you. Dr. Rubin?

**DR. ERIC RUBIN:** I wanted to get at the point about clinical efficacy testing. It just takes a long time, and the way that we've come, and the manufacturing process, it was already heard about, is going to take just far too long. We hope that in some of the current trials going on with multivalent vaccines that we see broad protection. And we hope that that happens. But right now I think that we are going to have to rely on immunobridging and remembering that immunobridging is not great right now. What's even worst is that it's not as good for protection of severe disease, which our

primary goal with the current vaccines is.

So, I don't think there's any way around the fact that if we're going to do this in a timely fashion, we're going to have to use safety and immunogenicity as our endpoints, and not have the clinical data that we'd all love to have. I don't think it's going to be practical.

**DR. ARNOLD MONTO:** This is why I raised the question about a new variant and getting clinical data, because it's not going to be possible to do that especially if we don't have transmission of that variant. Dr. Levy.

**DR. OFER LEVY:** Thank you. I think we're looking at a conundrum here, and people are putting their finger on it that it's going to be hard to generate all the data we want in short order when a new variant emerges. And, so, as Dr. Rubin said, the practical path is to go with safety and immunogenicity. But this leads us to the conversation about correlates of protection. And, yes, if the question is are sophisticated efforts ongoing around the world to

understand the correlates of protection? The answer, of course, is yes.

But the question to FDA is, what is the interoperability of this correlates of protection data? Are people using standard operating procedures? Is there data harmonization? Are people looking not just at the level of antibody but the types of antibodies functionally that are made? That's called system serology. Is there a public repository being developed by FDA or federal officials to put in the identified quality assured COP, correlate of protection data, so that there can be a meta-analysis of it?

We need to also keep our options open. MRNA vaccines are great. They can be turned around quickly. But it may be that other platforms emerge that give broader protection. So I would say as we move forward, we don't want to bake in a system that excludes other types of vaccines. Adjuvanted subunit vaccines, pan-coronavirus vaccines, for example, the nucleoprotein of the coronavirus might induce T cell responses that can mitigate severity of disease.

And we mentioned the global view, yes, the virus can be regional and our first priority is the United State. But, of course, our decisions will impact what's available for the rest of the world, and if they don't have the vaccines they need those variants that emerge there will come back here. The cycle time for new variants can be every three to six months. And what would the vaccine uptake be? Who would be willing to take vaccines that frequently? That's a question. So is this something that is just targeted to vulnerable populations potentially? And if we have a vaccine emerge that prevents infection, and reduces transmission, that'll change the decision process. Which population is driving the spread of the infection?

Finally, if the vaccine efficacy is mostly against severe disease and mortality, it seems we prioritized older adults, those with chronic diseases, and immunocompromised. So, those are my thoughts. Thank you.

**DR. ARNOLD MONTO:** And just to add, for all the years we've been working on influenza, HAI antibody is

not really a correlate of protection. And it was real poorly (audio skip).

**DR. OFER LEVY:** Exactly. We're at risk of doubling down on a failed strategy. We've got to get into the immunology. Yes, there are great labs out there doing amazing work, but where is the federal effort to coordinate all of that to develop a public repository around the correlate of protection, and to make sure we have the best available data for the immunogenicity when we make those decisions?

**DR. ARNOLD MONTO:** Dr. Sawyer.

**DR. MARK SAWYER:** It's not probably in the purview of VRBPAC, but I just want to point out that as new vaccine products start to be rolled out presumably their availability will be incremental. And so we are again going to have to face prioritization of who should get the vaccines first, and work through that at the initial release. So I'll just put that out on the table for us to remember.

**DR. ARNOLD MONTO:** Dr. Berger.

**DR. ADAM BERGER:** I think I agree with much of

what's been said. But I wanted to push on one concept. What we've been talking about is sort of putting this into the framework of how we deal with influenza. And our trying to predict what the next circulating virus is going to be. And make sure that we have a vaccine that is targeted specifically to that. And I think what we've seen, yeah, we've gone through Alpha, Beta, Delta, Omicron, and this has been a couple of years now, without seeing a concomitant decrease in efficacy against severe disease.

And so, we heard earlier that the mutation rate is something like five times the rate of flu at the moment. And, it's unclear how often we'll get that Omicron like variant that pops up. And so, I think we have a lot of unknowns at the moment to be making determinations about needing, for instance, to go ahead and make a specific vaccine that is directed at every potential variant that arises. Considering you're getting 12 mutations per year at this point. I'm going to put out something where I'm just going to put it out as a question to the committee.

Do we actually need to do this in advance, or is this something that you could be evaluating after the fact, and start developing the clinical data to support a change once we know that there are actually significant effects on something like severe disease or severe outcomes, as opposed to being preparatory for every potential variation that might arise in a given year?

It really is a question, but it's just because we're really thinking, or at least I'm hearing a lot of thinking, that it's tied to the way that we deal with flu. And I'm sorry, I can't remember who mentioned it earlier but we may not be dealing with the same type of ideology that we're dealing with flu when we're talking about COVID. So, I'd like to just give that idea like maybe we could actually do this after the fact and make correlative changes based on actual knowledge of impacts on clinical outcomes.

**DR. ARNOLD MONTO:** Dr. Mark, how are we doing in terms of helping you with our discussion? And how can we do better?

**DR. PETER MARKS:** Now, I actually think you're doing an excellent job. I think that we've heard some of the challenges here. And I think actually the open public dialog here about some of the challenges here, in coming to select something, is exactly what I think is important to have. We're going to have to think about this in a way that is less than optimal, because we're not going to have all the data that we'd like to have.

The Immune correlate of protection issue is one we very much understand. We've been watching and working with our NIH colleagues that have been trying to work through this, as well as the companies. There is not a clear, perfect, immune correlate of protection, and so we're using poor man's immune correlates of protection here -- or poor person's immune correlates of protection with antibody levels.

We do know, increasingly, the importance of the T cell response. But it hasn't all been integrated yet. And so, we are in a place where I think it very much take to heart, I think, what we've heard here both in terms of wanting to have data, wanting to have a

strawman proposal, wanting to have a unified composition, and then wanting to try to advance the correlates of protection as much as we could or can, to be able to make better decisions.

So I think that has done quite well here. I think the question of what conditions would indicate the need? It seems like we're saying that that would be data-driven. And, if I heard correctly here, it's basically data-driven and particularly data-driven by reduction in protection against severe outcomes, or the prediction that we would have reduction protection against severe outcomes. But I'd be happy to have people comment more on that.

But, in general, I think the committee's input is very much appreciated. And I think you've gone through a lot of the topics. I'd open it up to Dr. Weir and Dr. Fink, if they have other thoughts about questions they might like to ask directly.

**DR. ARNOLD MONTO:** Yeah, I think that one of the messages that's very clear is that severe outcomes are what really worry people. And, in fact, the fourth

dose was really predicated on evidence of beginning reduction in severe outcomes and not issues of transmissions, because transmission was really increasing even with the fourth dose.

I'd like to make us feel a little more comfortable about dealing with COVID and not flu. And remind people that with COVID, one variant seems to triumph over all. And, we typically are dealing with one variant at a time. A couple of years ago we had an AH1N1 virus with maybe four different variants circulating in the United States, and with efficacy being different for each. So, at least, we got that to work with with this virus, which does seem to mutate in a different way. Dr. Weir?

**DR. JERRY WEIR:** So, a couple of things. One, I also think the committee has given us a lot of nice thoughts and good ideas. Two questions for the committee to think about. One is, what do the members think about this idea that -- right now we have sponsors/manufacturers coming to us with proposal for how to evaluate composition, strains, things like that.

What about this idea of trying to better coordinate that? Not get the proposals directly from the manufacturers, but somehow coordinate the studies that need to be done to inform strain selection. Whether that NIH, CDC, I don't know who, but somehow coordinate that in advance. Would the committee think that's a good idea, and if so, maybe we could kick that around about how best to implement it.

And then my second question was -- and this is what I think I heard, but I want to make sure I heard it and didn't make it up. Does the committee think that getting back together in some reasonable period of time to review the available data is a good idea? Available data being mostly, not only whatever the epidemiology is in another month or two or three, but also the results of whatever clinical trials we do have with variant vaccines and different composition. So a couple of those things are what I'd like to hear a little bit more about.

**DR. ARNOLD MONTO:** Well, let me respond and then we'll open things up for the committee to respond

on their own. I think we've heard a strong feeling that we need more information on clinical trials that are ongoing. That this was one of the things we heard allusions to, but not a specific description of them, of multivalent trials, trials with some of the variants that have not taken off, which might be more central in terms of providing broader protection. So, that's one thing I've heard from the members.

The other thing which I think, again I'm going to ask the members to comment on is that, yes, we do need more attention to some of the various issues which are interagency, but the usual problem with those issues is a way to make them work. And I don't know that this committee is in the position of discussing interagency attention to some of these very broad issues which may be more in the hands of NIH or CDC or BARDA.

So let's have some discussion about those issues. I see Dr. Marasco got his hand raised. Dr. Marasco.

**DR. WAYNE MARASCO:** I'll make it brief, but I think, you know, we've been able to boost ourselves to

protection here with the ancestral Wuhan strain. So, it's not like that vaccine has not worked. And, vaccine effectiveness and efficiency, I think, is really what we're looking for, in hospitalization and severe illness.

But even if we give another booster vaccine, the vaccine is going to wane. So, we're going to be looking at waning immunity matter if we get another bivalent vaccine, or another vaccine. And I think we have to take into account the timing after vaccination when we look at these VE data.

Regarding interagency communication, there's a lot of ongoing studies that I think are really not under the purview of either our committee or the FDA that could bare a lot of insight into correlates of protection and things that we should be looking at that we don't have available to us right now. So I think that's something that the FDA and our committee could sort of put together to make these meetings more informative for that particular set of data which we're lacking.

**DR. ARNOLD MONTO:** Thank you. Dr. Offit.

**DR. PAUL OFFIT:** Right, I actually agree with you, Arnold. I think that the first step is identifying that there has been a variant that has arisen that has mutated those epitopes that are -- what have to date been fairly conserved epitopes that have been recognized by memory cells that has mutated away from that to the point that we're no longer protected against serious illness, however we define that.

And that has to come, I think, through the CDC, perhaps in collaboration with World Health Organization and other international bodies to see when that arises. And then what has to happen from that point on is a coordinated effort between FDA, NIH, et cetera, to help -- and the companies, on how to best move forward. I feel like at some level the companies kind of dictate the conversation. You often hear that the company now has an Omicron specific vaccine, or a vaccine that can now link with the influenza vaccine. And it shouldn't come from them. It really has to come from us.

The second thing is that, again, not to harp on

this boost thing. I know Peter said we could use the word "Joe," but I prefer to not use either. I think that typically you're not very good at boosting memory. I mean, if you look at John Wherry's data, what he finds is that after the first two doses given close together you get a high memory response, which is fairly long lived. But with that third dose you don't get a huge boost in memory. And, so, therefore, if you're going to have a variant that is so different from the current strains where you're not protected against impurities, that's another vaccine. That's a new vaccine.

And, therefore, we're going to have to think about how we're then giving this primary series again -- is it a two-dose series, is it a three-dose series. It could be a two-dose series 12 weeks apart instead of two doses close together. So, those are the things I think we're going to need to think about. Thanks for giving me time.

**DR. ARNOLD MONTO:** I surprisingly do not see any hands raised at the moment. I think I can speak for the committee because they are willing to appear and

spend a whole day listening to this material that we will meet as needed. And certainly it looks like it's something that will need follow up when we have more data available. I see, Dr. Cohn?

**CAPT. AMANDA COHN:** Thanks, Dr. Monto. So, I just want to comment on a couple of the things that has been said throughout this period. The first is I absolutely agree that it would be incredibly helpful, what Dr. Weir said, for the companies or for FDA to at least bring to the committee some of the different approaches the companies are thinking about taking or allowing us to comment on specific concepts so that we can better inform the direction moving forward.

I also just want to talk a little bit about this whole issue of severe disease, vaccine effectiveness, and waning immunity and durability. So, we have a great vaccine effectiveness platform in the United States. We're doing multiple different studies, as Dr. Ruth Link-Gelles described earlier. But we're never going to get the kind of specificity that I think everybody would like to see. And I just want to caution

people, these studies will show different numbers, it's different groups of people that are being studied, different circumstances, different outcomes. And, it is the totality of the evidence that I think helps inform our decision making.

But I think that when we start to see small declines, like for example 90 percent protection against hospitalization versus 88, I would caution people from jumping to big conclusions about that data. And, I do think we still have to recognize that there are confidence intervals around all of these individual studies. And when we jump to conclusions too quickly, we can find ourselves potentially jumping the gun a little bit.

And so, when we use the U.S. data, which I do think it's important to use U.S. data, I think that data from other countries can be really helpful and informative. But we can't just look at relative effectiveness, we need to look at the effectiveness of three doses compared to not getting vaccinated or two doses. And the effectiveness of four doses compared to

not getting vaccinated or two doses.

I think that when we talk to the public about relative effectiveness, it can misstate the overall protection that the primary series and booster dose, the three-dose series, does provide. And, we still have such a problem in this county with such a limited number of people having gotten their third dose that I feel like when we start talking about the importance of future doses we're forgetting that we need to get the country that third dose. And so we have really good data to tell us that vaccine effectiveness is improved against serious disease with that third booster dose. But, we also are seeing that that third dose is holding very steady.

And so, I would hate for us to use signal of potential reduction in VE to jump ahead and switch vaccine or to add another booster. So while I think there's this balance of needing to be prepared and continuing to work on getting a multivalent product that could be used-ready. I think that it would be helpful for the committee to describe or talk about some

specific conditions that would support the need for an updated booster dose.

For example, is the expectation that vaccine effectiveness is going to stay above 90 percent against hospitalization and death, or is it 80 percent? And, what is our threshold for wanting a booster. And then, from a durability prospective, if that booster only provides protection for eight weeks, as some of the data from Israel is showing, is that an effective use of additional intervention strategies.

And so, I think, we can talk a very long time about the complexity alone of the vaccine effectiveness data, but I think that it does need to be understood further by the committee, and honestly by the public, to help inform needs for future doses. Thanks.

**DR. ARNOLD MONTO:** Thank you, Dr. Cohn. What is the alternative if you find that a booster dose boosts only for eight weeks?

**CAPT. AMANDA COHN:** That's what the committee needs to discuss. I think it would be helpful, from my perspective, to hear from other committee members what

our expectation of the program is. This goes back to, I think, what Dr. Nelson was saying at the very beginning. What is the --

**DR. ARNOLD MONTO:** What would your expectation be? If we're in a situation where we need boost every eight weeks in order to keep protection up and that's not feasible from a public health standpoint.

**CAPT AMANDA COHN:** I do not believe that boosters every --

**DR. ARNOLD MONTO:** What's your thought?

**CAPT AMANDA COHN:** Yes, so I do not believe that boosters every eight weeks or even four months is a long-term strategy for prevention. But I think that given that our effectiveness against hospitalization in an immunocompetent individual is over 80 percent, and that's in older adult, and in persons with chronic medical conditions, I think we may have to accept that level of protection, and then use other alternatives ways to protect individuals with therapeutics and other measures.

**DR. ARNOLD MONTO:** So, would that be your

proposal then? I'm trying to get some concrete guidance. Would 80 percent be the level we would be shooting for?

**CAPT AMANDA COHN:** I think that we just need to have transparent conversations about levels that we're talking about. I said 85 to 90 percent. The vaccine appears to be about 90 percent, 88 percent effective against hospitalization. As I said, those numbers are not specific so I do think that that doesn't --

**DR. ARNOLD MONTO:** They (inaudible).

**CAPT AMANDA COHN:** Right. So, I think it would be helpful conversation, though, to hear from the other committee members where people's thresholds are. Because I think that it varies probably.

**DR. ARNOLD MONTO:** Dr. Marks?

**DR. PETER MARKS:** One of the things that we shouldn't forget about is that, yes, I think we're very much on board with the idea that we simply can't be boosting people as frequently as we are. And I'm the first to acknowledge that this additional fourth booster dose that was authorized was a stop-gap measure until we

got things in place for a potential next booster, given the emerging data. And it was done because of the amount of harm that has come to our older population in the United States, with one in 100 individuals over the age of 65 having died in the past two years of COVID-19. So we need to protect that population.

That said, moving forward, we will have this issue that coming into the fall season only half of the population overall, and granted it's two-third of the population over age 65 are vaccinated with a third dose, but half of the population overall has received a third dose and that means that they will not have the more durable protection. And the question is -- for those people even that's a lot of vaccines -- do you modify your vaccine composition so that when you do boost those people you give them the best chance at having a longer lasting protection given that we have seen the pandemic evolve.

I am completely of the mind that we have to do tremendous work in researching more advance vaccines, mucosal vaccines, pan-coronavirus virus vaccines, but

we're not going to get there for this coming year. And so this is really trying to do the best we can with the knowledge we have at hand, which is something that we've had to do a fair amount of over the past two years as a public health agency.

**DR. ARNOLD MONTO:** In calling on Dr. Levy, let me apologize for not calling on some people who are way down on my list. My system doesn't seem to be doing what it's supposed to be doing and bringing up those who have their hands raised. And above those that have their hands raised I have FDA Studio Cloud, and something else.

**MR. MICHAEL KAWCZYNSKI:** Why don't you take the person who hasn't spoken recently?

**DR. ARNOLD MONTO:** Dr. Kim.

**DR. DAVID KIM:** Thanks very much. Mike, I appreciate that interjection. I'd like to mention a couple of things. A lot of these discussion points have been touched on a number of times. And, I want to start out with Dr. Gans' comments earlier. She mentioned several things, us needing to understand the evolving

science, obviously. And this has been mentioned by multiple people, us also needing to better understand correlates of protection as well as understanding what's in the pipeline for new technology.

And those thoughts have been echoed by others, including Dr. Levy, and I think those are perfectly relevant and important questions. And this VRBPAC meeting, the slide we have here, Topics for VRBPAC Discussion. A lot of questions have been posed to us as VRBPAC members, but I think many of our discussion points have basically come around and we're asking FDA questions for discussion. So questions are begetting additional questions.

And I'm not sure if, given the topic and given the evolving process of this entire COVID-19 response including vaccination and therapeutic and others, whatever decision we make is appropriate, perhaps, for now. But it may not be appropriate three, six months down the line. So, I just wonder about the value of specifically answering, like what Dr. Cohn has tried to do, for what's on the table presently.

So I might propose that following Dr. Meissner and Dr. Sawyer's leads that we might step back and look at things a little more comprehensively, at a little higher elevation, if you will. And, the first issue has to do with the vaccine itself, vaccine and vaccinology. And the second issue is vaccination, meaning vaccine supply, manufacturing, and distribution concerns. And the third thing is basically an evaluation of the process that CDC is well positioned to do.

So, I'd like to address the first two items here. And, I'm doing that just in the context of VRBPAC mechanism. Presently, we meet on an ad hoc basis when the meeting's called every several months or more quickly if a vaccine is in the pipeline for approval -- or application for EUA or a BLA. But these issues, the issues that we see on the slide here, they're ongoing. So, I might propose that -- and I'll prefix it by saying there are different federal advisory committees that operate differently. VRBPAC has its own mechanisms. ACIP has another. And there are various non-immunization advisory committees that have their own

systems in place. And, for VRBPAC it seems that we simply call for a meeting when there are issues such as what we're doing today, or when there's an application that needs to be reviewed.

I'm going to propose that we stand up subcommittees so that we have an ongoing dialog, ongoing exchange of information with people and organizations that have data so that we have a process in place to consider these different questions. And, of course, over time that's going to -- the nature of the conversation will evolve. But I'm going to suggest that we stand up two subcommittees.

A first committee is vaccine composition, for obvious reasons. I think it includes the majority of the bullets identified on this slide. So we're talking about COVID epidemiology in the United States as well as globally. We're talking about vaccine strain composition and selection. And also, I think, this was brought up earlier, a contingency plan against poor vaccine effectiveness, be considered by the subcommittee.

And the second subcommittee that I might propose is vaccine supply and distribution, for obvious reasons, to review the current vaccine platforms, manufacturing capacity, et cetera, et cetera. That way we have an ongoing review, ongoing dialog, exchange of information so that we're better prepared to address these concerns over time. Because, right now, the situation is evolving and we should evolve with it. And I don't think we can optimally do that on ad hoc bases.

And if I may mention one other thing about semantics of the boost, booster shots, primary series, third dose, et cetera. I think the notion that it's just semantics is probably not going to serve us well. That it's important in the context of public affairs, public interface and clarity and communications. And I do wish that VRBPAC, as well as FDA, CDC, and others as they have been doing, pay much closer attention to semantics. Because I do think semantics are very important in how we present the information to the public. Back to you Dr. Monto.

**DR. ARNOLD MONTO:** Thank you. You've raised

some very interesting suggestions. I thought about some of them and they are very different from the way VRBPAC typically works with subcommittees. Dr. Marks.

**DR. PETER MARKS:** I think the best thing here for Dr. Kim's suggestion, because some of this is not even chartered for this committee, would be to take this back and have a discussion at a later time on this. We can even bring it back to the committee at a further time once we understand legally what we can do on this committee as well. Thank you.

**DR. ARNOLD MONTO:** I think we're in unchartered territory because with SARS-CoV-2 a lot of things have happened that have never happened before. Dr. Fuller, I apologize for missing you until now, please.

**DR. OVETA FULLER:** Thank you. So, let me first of all agree with Dr. Monto that we're in unchartered territory. And, secondly, I want to commend the FDA for pulling us together today. And the reason is this, as my colleagues have said, is a very complex situation. I don't think the public really understand how complex it is, and I don't even think we have understood until a

number of things came up today. I kept my hand up for a while, so let me try to walk through these really quickly.

**DR. ARNOLD MONTO:** I know you have.

**DR. OVETA FULLER:** To Dr. Weir's question about coordinating effort, and I think some of my colleagues have addressed that. Yes, please coordinate so that what happens is not being determined by companies coming to us. But that someone, whether it's FDA, NIH, CDC, WHO, whomever, would be helping to put out what's needed so the companies can help address that.

Secondly, should we convene more often? Yes. That's been addressed, because as Dr. Kim just brought forth these are complex questions. And we will need to know what's happening. And then third, as Dr. Monto just mentioned, and many of the people that came on the open forum, there are so many things that are changing and things we don't know. Example, the viruses are changing. We don't know what will happen. We have models that help us predict and we have surveillance that helps us look at what is happening. We have waning

immunity; we don't know what will happen with the strains that come up. But we do know that the current vaccines do protect well, as long as there's a reasonable time of boost, against hospitalization and death. And that's really, really important. So, we're going to have to learn as we go.

We also don't know the systemic effects of COVID. We still have long COVID. And clearly we still have rare but very real vaccine effects. And let me say to that, that's not only for COVID but we've seen those with other vaccines. There are people who have adverse, rare adverse, but serious effects to many vaccines including influenza.

So, because we're having so many more vaccines to COVID, we're seeing many more severe reactions that may be not only due to the vaccine but some other things. But those can't be run by, because they affect people's perception of what happening. So, we need continued research on that.

And then finally I want to ask a question of the FDA. We are here with COVID, two years into this.

We've used influenza as a somewhat model, not a perfect one, but let me remind us that we didn't get to understand influenza in two years. It's taken years to get to a uniform, somewhat still imperfect, but also useful process for what we do with flu.

So, the question is how much time has it taken to get to, and what has been the process for perhaps even less complex viruses, like getting to a vaccine and a program for HPD, or for influenza or for other vaccines? We need to remind ourselves to step back to say we are very new in this pandemic. And we don't have the answers. VRBPAC doesn't have the answers. FDA doesn't have the answer. The important thing here is that the public understands how complex this is, and that everyone is trying to be transparent and to do the best we know that we can learn in the time we have. So I'd like to put that to Dr. Marks, please.

**DR. ARNOLD MONTO:** Thank you Dr. Fuller. And, a couple of years ago we observed a six --

**DR. OVETA FULLER:** That's a question for Dr. Marks.

**DR. ARNOLD MONTO:** -- a sixty-fifth anniversary of the flu program. So, there's a lot of difference. Dr. Marks do you have responses?

**DR. PETER MARKS:** Dr. Fuller, what order would you like me to try to -- what questions do you like me to try to respond to here?

**DR. OVETA FULLER:** Well, first of all, let me say thank you for convening the panel now, so we can all -- not only the panel members -- but the general public can really get an idea of what FDA is dealing with. This is so not simple. So, I guess, what do you think is the highest priority? We know that a winter serge may come and there needs to be some plan for the winter. Is that your highest priority at the moment?

**DR. PETER MARKS:** Thanks for that question. First of all, let me thank you for what you said actually about trying to have this VRBPAC. I really appreciate your bringing that forward because that is exactly one of the reasons why we decided to have this meeting. Because we do think that it's important for the public to understand the complexity here and the

lack of absolute certainty. So really appreciate that.

In terms of what really keeps me up at night, it's the knowledge that we can't keep boosting. And that we're going to have vaccine exhaustion -- and I'm not talking about immune exhaustion. I'm talking about physical exhaustion of people not going to get boosted. So, if we have another chance for this coming winter, I think the idea here, at least one of the issues that we were, I think, some of the data seem to point to is that there is some concern that as we come into the November timeframe, that may be the time -- the October, November timeframe -- may be the time to try to boost again if the committee is in agreement when we talk about it more, in order to protect against a wave that could come at the highest time that we are at risk for kind of respiratory viruses going inside again.

I think from what we can see also from modelling exercises that have been done of waning of protection against severe disease, particularly for those who have only received two doses, and perhaps even for some who have received three, that would be a time

when I think we think people might be at greatest risk. So this is I think our area of highest concern, but we bring this to the committee because we also are interested in knowing if it's your highest concern as well.

**DR. OVETA FULLER:** Yes, thank you.

**DR. ARNOLD MONTO:** Thank you.

**DR. OVETA FULLER:** I guess my highest concern is protecting people for what we know happens. We know COVID can lead to death and hospitalizations. And we know the current vaccines protect against that. But we need people to understand that that's not the end all and that's not the magic formula, unless they take that and that also there's some risk involved, but the risk of the disease, as we've said multiple times, is much worse than the risk of the vaccine. This is not a perfect system. We've never been here before. We're all working together to do the best we can. And it's very complex. So I'll just stop there and hope that we can convene more often and be kept up to date with what is being discovered.

**DR. PETER MARKS:** Thank you for that.

**DR. ARNOLD MONTO:** Thank you. I just want to be sure that everybody I see with a hand raised actually wants to speak, because my system has been a little erratic. Okay, Dr. Cohn, is this a new raised hand?

**CAPT AMANDA COHN:** Sorry, no, that was not a newly raised hand, but I do just want to thank Dr. Fuller because that was very well said.

**DR. ARNOLD MONTO:** Very good. Dr. Levy.

**DR. OFER LEVY:** Just a brief point to remind folks that just a year or two ago we had nothing. And any vaccine that had some safety and even modest efficacy would be a godsend. So, right now we have to deal with what's in front of us, and the main platform in the coming year will be the MRNA vaccines. And thank God we have them. But as we move forward, and as Dr. Kim said, new structures -- I agree with him 100 percent -- will need to be put together to more systematically address the needs here including the immunogenicity correlates of protection. And give better or more specific guidance to the manufacturers of a range of

vaccines.

And the word has to get out to the political establishment, to the people of the United States, that more research is needed to have vaccines that don't require so many dosages or that offer broader protection. Because I don't think a lot of people have gotten that message either. So, there are a lot of different types of work to be done here. And, yes, we want to keep our eye on what's practical in the coming year, but we also want to be ambitious toward the future because maybe in a year, year and a half, or two years we can have something even better. But we're going to get there by working together in a systematic way. Thank you.

**DR. ARNOLD MONTO:** Dr. Wharton.

**DR. MELINDA WHARTON:** I'd really like to thank our colleagues at FDA for organizing this discussion. These are interesting -- these are really very important questions and discussions. And I'm glad that FDA has convened VRBPAC to discuss them. I guess what has struck me over the course of the day is even though

we've got a well-established process that works really well for influenza, there so much more unpredictability and unknowns as was acknowledged in Dr. Weir's presentation that it is an imperfect model.

And, one example of it not fitting exactly where we are is the fact that it doesn't sounds like WHO is going to be in a position to provide the direction that normally they provide two times a year for the influenza process. And, yet, in spite of that, given the timelines, we anticipate it seem like if something is going to be decided or recommended it's going to have to happen relatively soon.

And I did think it's reasonable to be concern about the winter given both waning protection and potential anticipated changes in circulating viruses, as well as the expected winter seasonality for respirator viruses. It doesn't seem like it's feasible to create a type-specific vaccine in a timeframe that would allow it to be used for a rapidly circulating variant like Omicron did. So, it does feel to me like the strategy that ultimately is going to be most effective for us is

how to use the vaccine technologies that are currently available, to hopefully create broader protection that will provide protection against a variety of variants, given that we can't really predict what's going to circulate.

But, interesting and important and complex questions, and it also make sense to me for FDA to be pretty directive to industry about what they would like to see soon to really facilitate that decision making. Thanks.

**DR. ARNOLD MONTO:** Thank you, Dr. Wharton. I'm going to close the list which I have now. People who have their hands raised, I have Dr. Meissner, Dr. Bernstein and Dr. Kim. And so we can ask Dr. Marks after that whether he thinks we've got enough opinions and recommendations to move forward, so Dr. Meissner.

**DR. CODY MEISSNER:** Thank you, Dr. Monto. We've got so many topics circulating here. And I have a few thoughts about separate issues. And the first, before I forget it I wanted to thank Dr. Marks and Dr. Fink for the briefing documents that they circulated --

and it's on the public website -- before the meetings, because I found those very helpful and I suspect a lot of time has been spent on that.

Then, the first point I want to make is we haven't spoken -- well, I guess, actually Paul raised the question about the number of dosages and the interval between dosages, and, the concentration of MRNA in the different vaccines for different age groups. Because the data from the New York Department of Health pointed out, I think, that that's really a critical issue. The twelve-year-old children that got the 30 mg dose had considerably longer protection than the eleven-year-old children who got 10 mg dose. So, I realize how complicated this is, but I just raised that as another issue that needs to be considered going forward.

Then, in terms of the issue of how will we decide when a vaccine needs to be modified. What is going to be the threshold of which we say, gee, it's so much escape from vaccine immunity that we need to change? Such a difficult question to answer, but hopefully we're going to be able to convert this into an

annual vaccine that will be given, perhaps, at the same time as a combination vaccine with influenza and maybe RSV in time, because I agree there's wariness if we continue to recommend frequent boosting.

And, I think we need to stay away from herd immunity as the threshold, and I think everyone agrees that that's not going to be a reasonable definition of vaccine efficacy. Because until we get vaccines that can be applied to mucosal surfaces, we're probably not going to get a degree of herd immunity that we want.

And then the final point I wanted to make is I tend to agree with the idea that there's a difference between waning immunity and a variant strain that isn't susceptible to vaccine induced immunity. And I wonder if it might be more helpful for the public to understand this difference. Because those are different reasons that we would want to vaccinate people. Thank you.

**DR. ARNOLD MONTO:** Thank you. Yeah, the difficulty is to separate out the waning from the strain specific differences.

**DR. CODY MEISSNER:** I understand.

**DR. ARNOLD MONTO:** Dr. Bernstein.

**DR. HENRY BERNSTEIN:** Thank you, Dr. Monto. This has been a wonderful conversation. And lots of details still to be fleshed out. And we don't have a lot of time to do so, but it was a wonderful conversation. I do think that we still need to get more people vaccinated. And it seems quite obvious that those who were vaccinated do better than those that are unvaccinated when we look at all of the outcomes.

And I think it's imperative of us to clearly communicate to the public what we're thinking and what our overall aim is. And I would suggest that our overall aim is to prevent severe disease, hospitalization and death, more than just infection prevention. And I think people need to also -- public needs to understand that there are multiple individual factors that come into play such as the number of dosages of vaccine they've already received, could be zero, it could be four, their age, their underlying medical conditions, their immune competence, and even their work responsibilities.

So I think this was a great conversation and more to come. And we need to continue to communicate this clearly to the public. Thank you.

**DR. ARNOLD MONTO:** Thank you. Dr. Kim.

**DR. DAVID KIM:** It's been said about two or three times something about interagency communication regarding immunization or vaccines. And I just want to put this information out for the benefit of VRBPAC members that the communication between federal agencies has taken place always, as long as I've been around working on immunizations. That through the Advisory Committee on Immunization Practices at CDC, through the Advisory Commission on Childhood Vaccines through HRSA and the National Vaccine Advisory Committee through the HHS. There's a format to which information exchange takes place.

And I might also mention that there is an interagency vaccine workgroup that's managed through the office of the Assistant Secretary for Health. That brings together about 16 different federal operations divisions such as CDC, FDA, NIH and so on, plus other

departments such as Department of Veterans Affairs, Department of Defense, et cetera. And, the purpose of that particular workgroup is to facilitate communication and collaboration amongst its immunization-interested members. So there is a forum through which this dialog takes place, between federal agencies. And if there are issues that VRBPAC members want to bring up to such a group, then the forum would be open to any of the members including CDC, FDA, NIH and obviously we're involved as well.

It's chaired by the Office of the Assistant Secretary for Health. And, so would be happy to take up any information exchange that might be needed, either for VRBPAC or any other function related to immunization.

**DR. ARNOLD MONTO:** Thank you very much, Dr. Kim. So, Dr. Marks you've heard that we are happy to undertake work going forward on this whole very complex issue, that we are concerned about the timeline, and are cognizant of the need to address the issues as they come up, that we would love to have a correlate of protection

but we don't have it. We realize that clinical trials data will be necessary, but we might have to use surrogates if that becomes necessary. Our focus is on preventing hospitalization and deaths.

We don't feel comfortable with multiple boosters every eight weeks, would love to see an annual vaccination similar to influenza, but realize that the evolution of the virus will dictate how we respond in terms of additional vaccine doses. That we would like to see 80 percent protection, but, again, with the development of antivirals and other therapeutics we realize you can't prevent everything, especially with an evolving virus. And the need for revaccination will really be dictated by the virus more than by us.

So, to you, Dr. Marks, have we fulfilled your expectations for what we could discuss in this kind of a situation?

**DR. PETER MARKS:** Yeah, thank you so much. I think you have done a great job and I think the committee members have all really done a great job putting various pieces out there. I think just if I can

say a couple of final words, I'd appreciate it. Is that okay, Dr. Monto? I think we have what we need.

**DR. ARNOLD MONTO:** Yes, please.

**DR. PETER MARKS:** First of all, I want to apologize for the technical difficulties today. I want to apologize to the committee members, to you, Dr. Monto, I know that we seem to have issues that I am told are related to the platform we were using. But we will do our absolute best to make sure that these are addressed for future meetings, because that creates a suboptimal experience both for the committee members but also for the viewing public who is trying to hear these meeting.

Next I just want to thank all of the committee members and our speakers for their participation today. The dialog that has happened over the past about two hours has been incredibly helpful to us in terms of how we go about thinking about the COVID-19 booster strategy. I also want to thank our staff for all of the tremendous work that they did in preparing for this meeting.

How we consider boosters for the broader population going forward is a very high priority for both FDA and our U.S. Government partners. And, the agency recognizes the tremendous interest in this topic, and it's committed to ensuring that our decision-making around boosters continues to be done in a transparent manner. And we want people to be able to remain confident in the safety and effectiveness of all of the COVID-19 vaccines.

Meetings like the one today really did provide us with an opportunity to collect and consider feedback from a variety of stakeholders. And in this regard we do anticipate holding another meeting on this topic of possible boosters for next fall to winter. And that meeting we assume will occur by early summer, so not too many weeks away. And that will get into a more specific level of detail regarding the composition.

At the end of our process, really our goal here is to stay ahead of future variants and outbreaks. And ensure that we do our best to reduce the toll of disease and death, due to COVID-19, on our population. So I

just want to thank everyone again. There's the saying, be careful what you wish for. I suspect that over the next few months there will be a fair number of meetings of this committee, not just for boosters but for other topics that may come up.

So, I really want to thank everyone and really enjoy and appreciate all the contributions today. Thank you.

**DR. ARNOLD MONTO:** Thank you, Dr. Marks. And over to you, Prabhakara, for the formal closing of the meeting.

**(PLATFORM AUDIO/VIDEO WAS LOST AT THIS POINT)**

**[MEETING ADJOURNED]**