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Center for Biologics Evaluation and Research (CBER)
167th Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting

OPEN SESSION

Web-Conference

September 17, 2021

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.	University of Michigan
Paula Annunziato, M.D.	Merck
Archana Chatterjee, M.D., Ph.D.	Rosalind Franklin University
CAPT Amanda Cohn, M.D.	National Center for Immunizations and Respiratory Diseases Centers for Disease Control and Prevention
Hayley Gans, M.D.	Stanford University Medical Center
Michael Kurilla, M.D., Ph.D.	National Institutes of Health
H. Cody Meissner, M.D.	Tufts University School of Medicine
Paul Offit, M.D.	The Children's Hospital of Philadelphia
Steven A. Pergam, M.D., M.P.H., FIDSA	Seattle Cancer Care Alliance
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.	Massachusetts Institute of Technology
Pamela McInnes, D.D.S., M.Sc.	National Institutes of Health (Retired)
Stanley Perlman, M.D., Ph.D.	University of Iowa
Jay Portnoy, M.D.	Children's Mercy Hospital
Eric Rubin, M.D., Ph.D.	Brigham and Women's Hospital
Mark Sawyer, M.D., F.A.A.P.	Rady Children's Hospital, San Diego

Melinda Wharton, M.D, M.P.H.	Centers for Disease Control and Prevention
SPEAKERS AND GUEST SPEAKERS	
Sharon Alroy-Preis, M.D., MPH, MBA	Ministry of Health, Israel
Ron Milo, Ph.D.	Weizmann Institute of Science, Israel
Sara Oliver, M.D, MSPH	Centers for Disease Control and Prevention
Jonathan Sterne, Ph.D.	University of Bristol, UK
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CDR Valerie Marshal, M.P.H., P.M.P	Food and Drug Administration
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Peter W. Marks, M.D., Ph.D.	Food and Drug Administration
Joohee Lee, M.D.	Food and Drug Administration
Jerry Weir, Ph.D.	Food and Drug Administration
Celia M. Witten, Ph.D., M.D.	Food and Drug Administration
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Mr. Michael Kawczynski	Food and Drug Administration

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OPENING REMARKS: CALL TO ORDER AND WELCOME

MR. MICHAEL KAWCZYNSKI: Good morning and welcome to the 167th meeting of the Vaccines and Related Biological Products Advisory Committee. I'm Mike Kawczynski. I will be moderating today's meeting. This is a live virtual meeting so we do have participants from around the country and around the world, and because it is a virtual meeting as many of you have experienced in the last few years, every once in a while we may run into a technical glitch where it may cause us to have an unexpected pause just in order to make sure that we have our members and all that back in the meeting.

So, if that happens, don't fret. We'll take care of it. But with that being said, I will have to jump in every once in a while just in case that does happen. So that being said, let's get this meeting started, and I'd like to hand the meeting off to our chair Dr. Arnold Monto, the acting chair. Arnold, you there? Arnold let's make sure we get you unmuted real

quick. I got you. All right, Arnold.

DR. ARNOLD MONTO: Okay. We'll get it right after a while.

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

DR. ARNOLD MONTO: I want to thank you for all your technical help and backup in this challenging time in terms of organizing meetings. Let me add my welcome to the 167th meeting of the Vaccines and Related Biologics Products Advisory Committee of the Center for Biologics Evaluation and Research. We have an important meeting to talk about a specific topic, and we are in open session to discuss Pfizer-BioNTech's supplemental biologics application for administration of a third dose or booster dose of the COVID-19 vaccine in individuals 16 years of age and older.

Welcome again to all the members. The ad hoc members and to the public. Let's get some of the housekeeping details out of the way first and also introduce our distinguished Committee. I'd like to turn it over to our designated federal officer, Prabha

Atreya, who will do this activity. Thank you, Prabha.

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

DR. PRABHAKARA ATREYA: Good morning. Thank you, Dr. Monto. 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 167th Vaccines and Related Biological Products Advisory Committee meeting. On behalf of the FDA, the Center for Biologics Evaluation and Research, and our Vaccines Advisory Committee, I would like to welcome everyone for today's virtual meeting. The topic of today's meeting is to discuss in open session Pfizer-BioNTech's supplemental biologics license application for the administration of a third dose or booster of the COVID-19 vaccine, Comirnaty, in individuals 16 years of age and older.

Today's meeting and the topic were announced in the federal register notice that was published on

September 7th, 2021. I would like to introduce and acknowledge the excellent contributions of the staff in my division and the great team I have in preparing for this meeting. Ms. Kathleen Hayes is my co-DFO, providing excellent support in all aspects of preparing for and conducting this meeting. Other staff who helped and contributed significantly on this are Ms. Monique Hill, Dr. Jeannette Devine, and Ms. Christina Vert who provided excellent administrative support.

I would also like to express our sincere appreciation to Mike Kawczynski in facilitating this meeting today. Also kudos to many FDA staff working hard behind the scenes every day trying to ensure that today's virtual meeting will also be a successful one like all the previous VRBPAC meetings on COVID topics. Please direct any press or media questions for today's meeting to FDA's Office of Media Affairs at fdaoma@fda.hhs.gov. Today's transcriptionist for the meeting is Ms. Linda Giles.

We will begin today's meeting by taking a formal role call for the committee members and then the

temporary voting members. When it is your turn, please turn on your video camera, unmute your phone and then state your first and last name. And then when finished, you can turn off your camera so we can proceed to the next person. Please see the Committee roster slide, in which we will begin with the chair. Mike, can we have the roster slide, please? Next slide please. Committee roster. Thank you. Dr. Arnold Monto, please start.

DR. ARNOLD MONTO: I'm the chair. Okay. This is Arnold Monto. I am a professor of epidemiology and public health at the University of Michigan school of public health. Prabha.

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

DR. AMANDA COHN: Good morning. Dr. Amanda Chon. Pediatrician at the Centers for Disease Control and Prevention.

DR. PRABHAKARA ATREYA: Thank you. Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Good morning,

everyone. My name is Archana Chatterjee. I am the Dean of Chicago Medical School and Vice President for Medical Affairs at Rosalind Franklin University of Medicine and Science in Chicago. I am a pediatric infectious diseases specialist and happy to be here this morning. Thank you.

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

DR. CODY MEISSNER: Thank you, Prabha. My name is Dr. Cody Meissner. I'm a professor of pediatrics at Tufts Children's Hospital in Boston.

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

DR. HAYLEY GANS: Good morning. Dr. Hayley Gans, pediatric infectious disease at Stanford University.

DR. PRABHAKARA ATREYA: Thank you. Next, Dr. Michael Kurilla.

DR. MICHAEL KURILLA: Thank you. Thank you, Prabha. Good morning. Mike Kurilla, I'm the director of the division of clinical innovation at the National

Center for Advancing Translational Science within NIH, background in infectious disease product development and pathologist by training.

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

DR. PAUL OFFIT: Yes, good morning. I'm Paul Offit. I'm a professor of pediatrics at the Children's Hospital of Philadelphia and the University of Pennsylvania School of Medicine.

DR. PRABHAKARA ATREYA: Thank you. Dr. Paula Annunziato.

DR. PAULA ANNUNZIATO: Good morning, I'm Paula Annunziato. I head vaccines global clinical development at Merck, and today I am the industry representative -- the non-voting industry representative for this meeting.

DR. PRABHAKARA ATREYA: Thank you. Next is Dr. Steve Pergam.

DR. STEVEN PERGAM: Hello, everybody. I'm Steve Pergam. I'm an associate professor in adult infectious disease at Fred Hutchinson Cancer Research

Center, University of Washington.

DR. ATREYA: Thank you. Dr. Oveta Fuller.

DR. OVETA FULLER: Good morning. I'm Dr. Oveta Fuller. I'm an associate professor of microbiology and immunology at the University of Michigan Medical Center and a member of the STEM Initiative of the African study center.

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

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

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

DR. JAMES HILDRETH: Good morning. I'm Dr. James Hildreth. I'm the president and CEO of Meharry Medical College and professor of internal medicine. Thank you.

DR. PRABHAKARA ATREYA: Thank you. Next, Dr. Jay Portnoy.

DR. JAY PORTNOY: I'm Dr. Jay Portnoy. I'm a professor of pediatrics at the University of Missouri, Kansas City School of Medicine. And I'm an allergist/immunologist at Children's Mercy Hospital of Kansas City, Missouri.

DR. PRABHAKARA ATREYA: Thank you. Next, we have Dr. Jeannette Lee.

DR. JEANETTE LEE: Good morning. My name is Jeannette Lee. I'm a professor of biostatistics and a member of the Windsor P. Rockefeller Cancer Institute at the University of Arkansas for Medical Sciences. Thank you.

DR. PRABHAKARA ATREYA: Thank you. Next Dr. Mark Sawyer. Dr. Sawyer?

DR. MARK SAWYER: Good morning. This is Dr. Mark Sawyer. I'm a professor of pediatric infectious disease at the University of California, San Diego and Rady Children's Hospital in San Diego.

DR. PRABHAKARA ATREYA: Thank you. Next, I would like to say that Dr. Peter Marks, Center Director, would like to say a few welcome remarks a

little later after we start the session and would also like to acknowledge the presence of Dr. Celia Witten, Deputy Director of CBER and Dr. Gruber, Director of Office of Vaccines, and Dr. Philip Krause, Deputy Director of the Office of Vaccines at this meeting. Now, I will proceed with reading the Conflict of Interest Statement for the public record.

MR. MICHAEL KAWCZYNSKI: Dr. Prabha, you forgot somebody. We have Dr. Wharton.

DR. PRABHAKARA ATREYA: Oh, I'm sorry. Dr. Melinda Wharton, I'm really sorry. Can you introduce yourself?

DR. MELINDA WHARTON: Good morning. I'm Melinda Wharton. I'm an adult infectious disease specialist, and I'm at the Centers for Disease Control and Prevention.

DR. PRABHAKARA ATREYA: Thank you. Now we will read the Conflict of Interest Statement for the public record.

MR. MICHAEL KAWCZYNSKI: Prabha, we still have some more temporary voting members.

DR. PRABHAKARA ATREYA: Okay. Thank you. Dr. Ofer Levy, could you introduce yourself? We can't hear you.

MR. MICHAEL KAWCZYNSKI: Ofer, don't forget to unmute.

DR. OFER LEVY: There we go. Good morning. My name is Ofer Levy, and I'm the director of the precision vaccines program at Boston Children's Hospital and professor of pediatrics at Harvard Medical School.

DR. PRABHAKARA ATREYA: Thank you. Next, Dr. Pamela McInnes.

DR. PAMELA McINNES: Good morning. Pamela McInnes. Past deputy director, National Center for Advanced Translational Sciences at the National Institutes of Health. Thank you.

DR. PRABHAKARA ATREYA: Appreciate it. Thank you. Dr. Stanley Perlman.

DR. STANLEY PERLMAN: I'm Dr. Stanley Perlman, the Department of Microbiology and Immunology at the University of Iowa in the pediatric infectious diseases

division.

DR. PRABHAKARA ATREYA: Thank you. Okay. For the public, this is the Conflict of Interest Statement. The Food and Drug Administration is convening virtually today on September 17th, 2021, the 167th meeting of the Vaccines and Related Biological Products Advisory Committee under the authority of the Federal Advisory Committee as of 1972. Dr. Arnold Monto is serving as the acting voting chair of today's meeting. Today on September 17th, 2021, the committee will meet in open session to discuss Pfizer-BioNTech's supplemental biologics license application for administration of a third dose or booster dose of the COVID-19 vaccine, Comirnaty, in individuals 16 years of age and older.

This topic is determined to be a particular matter in involving specific parties. With the exception of the industry representative member, all standing and temporary voting members of the VRBPAC are appointed Special Government Employees, SGE, or regular government employees from other agencies and are subjected to federal conflicts of interest laws and

regulations. The following information on the status of the Committee's compliance with the regulated conflicts 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, or SGE consultants of this Committee, have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouse or minor children and for the purpose of 18 U.S. Code 208, their employers. These interests may include investment, 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 are 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 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 these special government employees, for reasons, outweighs the potential for conflict of interest created by financial interests involved, or if the interest of regular government employees is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from their employees.

Based on today's agenda and all financial interests reported by all faculty members and consultants, there have been one conflict of interest waiver issued under 18 U.S. Code 208 in connection with this meeting. We have been following consultants serving as temporary voting members as we have seen before: Dr. Oveta Fuller, Dr. James Hildreth, Dr. Jeannette Lee, Dr. Ofer Levy, Dr. Pam McInnes, Dr. Arnold Monto, Dr. Stanley Perlman, Dr. Eric Rubin, Dr. Mark Sawyer and Dr. Melinda Wharton.

Among these consultants, Dr. James Hildreth, a Special Government Employee, has been issued a waiver for his participation in today's meeting. The waiver was posted on the FDA website for public disclosure. Dr. Paula Annunziato, of Merck, will serve as the industry representative for today's meeting. Industry representatives are not appointed as special government employees and serve as non-voting members of the Committee. Industry representatives act on behalf of all related industries and bring general industry perspective to the Committee. Industry representatives on this committee is not screened, does not participate in any closed sessions if held and do not have voting privileges.

Dr. Jay Portnoy is serving as the temporary consumer representative for this Committee. Consumer representatives are appointed special government employees and are screened and cleared prior to their participation in the meetings. They are voting members of the Committee.

Today's meeting has one external speaker from

the Centers for Disease Control and Prevention, CDC, which is Dr. Sara Oliver. The guest speakers of this meeting are Dr. Sharon Alroy-Preis, who is the Director of Public Health Services Ministry of Health, Israel, and also Dr. Ron Milo, a professor in the Plant and Environmental Sciences Department, The Charles and Louise Gartner Professional Chair of Weizmann Institute of Science in Israel. And Dr. Jonathan Sterne is a professor of medical statistics and epidemiology within the Bristol Medical School at the University of Bristol, UK. Disclosure of financial conflict of interest of 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 relationship that they may have with any affected firm, its products, and if known, direct competitors. We would like to remind the standing and temporary members that if any of the discussion involve any of the products that's already on the agenda, particularly if a participant has a

personal or imputed financial interest, the participant needs to inform the DFO and exclude themselves from such involvement and the disclosure, and their exclusion will be noted for the record.

This concludes the reading of my Conflict of Interest Statement for the public record. At this time, I would like to hand over the meeting to our chair, Dr. Arnold Monto. Dr. Monto, take it away. Thank you.

MR. MICHAEL KAWCZYNSKI: Dr. Monto, I think we have you muted right now. Hold on a second. Dr. Monto, when we get a chance, we're going to have you redo your camera. I think we have a little issue with your camera, but not to worry. Go ahead.

FDA INTRODUCTION

DR. ARNOLD MONTO: Okay. It's my pleasure to introduce Dr. Peter Marks, the Director of the Center for Biologics Evaluation and Research who will give us his opening remarks.

WELCOME

DR. PETER MARKS: Thanks, Dr. Monto. Good morning and welcome to the committee members, FDA staff, the sponsor and the public that's viewing this meeting today. This Committee advises the Agency in discharging its responsibilities as they relate to helping ensure safe and effective vaccines. Over the past year, the Committee has participated in some of the most important decisions made by the FDA in recent memory, contributing markedly to public health. Thank you so much for your continued service.

Also, tremendous thanks go to all of the FDA staff who have worked tirelessly through this pandemic to facilitate the availability of potentially life-saving medical products. Today, the Committee will consider the application from Pfizer for the administration of a third dose of their COVID-19 mRNA vaccine approximately six months following a primary vaccination series.

In preparation for the discussion, there will be introductory presentations relevant to the potential need for additional vaccine doses. We know that there may be differing opinions as to the interpretation of the data regarding the potential need for additional doses, and we strongly encourage all the different viewpoints to be voiced and discussed regarding the data which is complex and evolving.

It also requires near real-time analyses. We're committed to focusing on the science, and we'll drive our decision making -- and we'll carefully consider those data in the context of the clear and obvious public health need to continue slowing the spread of COVID-19, which at this time is leading to the death of close to 2,000 Americans each day.

That said, as we proceed, I would ask that we do our best to focus our deliberations on the science related to the application under consideration today and not on operational issues related to a booster campaign or on issues related to global vaccine equity. If we stray into those latter topics, the chair and I

will gently bring us back into the scope of this Advisory Committee meeting. I'll be present all day to assist, as necessary, and look forward to a very productive meeting. Thank you so much. Again, today we look forward to a very robust discussion. Thank you.

INTRODUCTION OF THE TOPIC

DR. ARNOLD MONTO: Thank you, Dr. Marks. I would like to introduce Dr. Marion Gruber, Director, Office of Vaccines Research and Review, who will introduce the topic. Dr. Gruber.

DR. MARION GRUBER: Well, thank you very much, and good morning and welcome. My name is Marion Gruber, and I am the Director of the Office of Vaccines Research and Review. This is likely my last VRBPAC meeting that I attend in my position as Director of the Office of Vaccines. I'm retiring from federal government service on October 31st, after a very fulfilling and rewarding career as a public health

servant at FDA, and for that, I'm grateful.

I would like to take a few minutes to thank the members of the VRBPAC, both past and present, for lending their scientific expertise over the many years that helped us to address many challenging and complex scientific and clinical issues pertaining to preventative vaccine development and to assure that the vaccines we license are safe and effective for their intended use. I also want to thank the American public, it has been a privilege to serve you. All of my actions and decisions over my 32-year FDA career have been grounded in science with you in mind and in the best interest of your health and safety, and I will continue to hold fast to these principles moving forward.

Now to today's topic which is the application for licensure of a booster dose of Comirnaty, COVID-19 Vaccine, mRNA. Can I have the next slide, please? On August 23rd of this year, the FDA approved Comirnaty for active immunization to prevent coronavirus disease 2019, caused by severe acute respiratory syndrome

coronavirus-2 in individuals 16 years of age and older when administered as a two-dose series three weeks apart.

On August 25, Pfizer-BioNTech submitted a supplement to their biologics application for Comirnaty seeking approval for administration of a booster dose approximately six months after dose two in individuals 16 years of age and older. The VRBPAC is convened today to determine whether the data submitted are sufficient to support approval of a booster dose of Comirnaty when administered at least six months after completion of the primary series for youth and individuals 16 years of age and older. Next slide, please.

The emergence of the highly transmissible Delta variant of SARS-CoV-2 has led to considerations of the potential need for booster doses for fully vaccinated individuals. Data from post-authorization effectiveness studies conducted suggest that the currently U.S. authorized or licensed vaccines remain effective in protecting against severe disease.

However, some data suggests that effectiveness may be waning. Concerns have also been raised that declining neutralizing antibody titers or reduced effectiveness against symptomatic disease may herald significant declines in effectiveness against severe disease. And you will be hearing an overview of some of these data in the next session. Next slide, please.

For a licensed COVID-19 vaccine, a change in dosing regiment to include a booster dose will require the approval of a supplemental BLA, and the supplement must include data that demonstrates that the additional dose is safe and effective. There is an expectation that demonstration of effectiveness of the additional dose is based on adequate and well-controlled clinical trials. However, findings of effectiveness of the additional dose, while necessary, is not sufficient for an FDA approval. A determination that the additional dose is safe for the intended use is also required. Next slide, please.

The evaluation of whether the additional dose is safe involves weighing whether its benefits outweigh

its risk. That means that available data should support the effectiveness of a booster dose, specifically against the currently circulating SARS-CoV-2 variants, and the benefit of the booster dose should be considered relative to the benefit already provided by the previous vaccinations with the primary series. Considering risks, available data should at a minimum characterize the most common adverse reactions that are associated with the booster dose, and uncertainties regarding benefits and risks are also considered. Next slide, please.

Post-authorization data demonstrate an increased risk of myocarditis and pericarditis, particularly within seven days following the second dose of Comirnaty. The observed risk is higher among males under 40 years of age than among females and older males. The observed risk is highest in males 16 to 17 years of age. It is not known whether there will be an increased risk of myocarditis/pericarditis or other adverse reactions after a booster dose of Comirnaty. Thus, risk-benefit considerations to

determine whether to approve a booster dose will need to be informed by the known and the potential risks of the vaccine. Next slide.

So to summarize, benefit/risk evaluations should take into account whether the booster dose will prevent severe cases of COVID-19, including those caused by currently circulating variants, in addition to those prevented by the primary series. The safety profile of the additional dose will also be considered. FDA's evaluation supported by VRBPAC of the safety and effectiveness data of a booster dose of Comirnaty in the age groups for which it is currently licensed is thus essential. This concludes my introductory remarks, and I look forward to a robust, transparent and evidence-based discussion. Thank you. I turn it back to you, Dr. Monto.

BACKGROUND

DR. ARNOLD MONTO: Thank you so much, Dr. Gruber. I want, as an individual and representing the

biomedical community, to thank you for your years of service. They really are appreciated and have been extremely valuable. Next, I'd like to turn over for further background for Dr. Ramachandra Naik from OVRR. Dr. Naik.

DR. RAMACHANDRA NAIK: Thank you. Good morning, everyone. My name is Ramachandra Naik from the Division of Vaccines and Related Products Applications in the Office of Vaccines, and I am the Review Committee Chair for this supplemental BLA. I am going to provide background for today's advisory committee meeting regarding Pfizer-BioNTech supplemental BLA for the mRNA COVID-19 vaccine, Comirnaty, for a booster dose in individuals 16 years of age and older. This is the outline of this background talk. This provides brief description of the licensed vaccine that is Comirnaty. An overview of Comirnaty supplemental BLA and the clinical package, an overview of today's agenda, and finally voting questions to the Committee.

Comirnaty was licensed on August 23rd, 2021.

This is the only approved COVID-19 vaccine in the U.S. The vaccine is indicated for prevention of COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older. Comirnaty is administered incrementally as a primary series of two doses, three weeks apart. Each 0.3 mL dose of Comirnaty contains 30 micrograms of a nucleoside-modified messenger RNA encoding the viral spike glycoprotein of SARS-CoV-2.

Topics for today's advisory committee meeting: the booster dose supplement to the BLA for Comirnaty. The supplemental BLA was submitted on August 25, 2021. It is a single 0.3 mL dose of Comirnaty containing 30 micrograms mRNA. It's supposed to be administered approximately six months after the second dose in individuals 16 years of age and older. The clinical package includes safety and immunogenicity data from approximately 330 participants who were reenrolled to receive a booster dose of Comirnaty approximately six months after completing the primary series of two doses. A breakdown of these subjects and details of the data will be provided in later presentations by

Pfizer and the FDA.

This is the overview of today's agenda. After this introduction and background, CDC's Dr. Sara Oliver is going to present the epidemiology of pandemic CDC Delta variants and breakthrough infections, followed by Dr. Jonathan Sterne's presentation. He's a professor at University of Bristol. He's going to present data on the overall effectiveness of COVID-19 vaccines.

Later Dr. Sharon Alroy-Preis, Director of Public Health Services and Minister of Health Israel, and Dr. Ron Milo, professor at Weizmann Institute, Israel, they're going to present the data from Israel, booster protection against confirmed infections and severe disease, followed by a five minute break.

After the break, Ms. Donna Boyce and Dr. Bill Gruber will provide applicant presentation, followed by FDA presentation by Dr. Joohee Lee, who is going to present the clinical data submitted to FDA by Pfizer.

After that, there will be a lunch break. After lunch, there will be an open public hearing followed by a short break. There will be a question

and answer session regarding the applicant and FDA presentations followed by committee discussion and voting before adjournment of the meeting.

This is the question to the Committee. Do the safety and effectiveness data from the clinical trial C4591001 support approval of a Comirnaty booster dose administered at least six months after completion of the primary dose for use in individuals 16 years of age and older? Please vote yes or no.

Thank you. That's the end of the background.

CDC: EPIDEMIOLOGY OF PANDEMIC CDC DELTA VARIANT/BREAKTHROUGH INFECTIONS

DR. ARNOLD MONTO: Thank you, Dr. Naik. Next, I'd like to turn over to Dr. Sara Oliver of the Division of Viral Diseases, CDC, who will update us on the epidemiology of pandemic CDC Delta variant/breakthrough infections. I assume that is CDC identified, not at the CDC.

I'd like to make sure that the speakers from

now on will stick to time. We are going to have some real problems if we go over because we have a very important discussion at the end of the day, and that's why I skipped questions that are on the agenda for Dr. Naik. We'll get to some of those later on. I believe we need very much to keep our focus on the next talks. Dr. Oliver, please.

DR. SARA OLIVER: Thank you so much and good morning. So today I'll look at COVID-19 cases and hospitalizations, COVID vaccines administered and COVID vaccine effectiveness. We'll look at estimates for VE over time, VE during times of the Delta variant, and VE for older adults. So first for COVID cases and hospitalizations, to date over 41 million cases have been reported in the U.S. This slide shows the trends in the number of COVID cases reported daily with the seven-day moving average in red.

As everyone is aware, we're currently experiencing a surge in cases second only to the surge seen in the winter. The current seven-day moving average is around 145,000 cases per day. This slide

represents the daily trends in the number of COVID-19 deaths per day in the U.S. The seven-day moving average around is 1,300 deaths per day. Then this slide shows the weekly trends in the COVID-19 associated hospitalization rates in the U.S. by age group. Rates have been increasing with this recent surge but are somewhat less than what was noted this past winter.

However, as we consider these rates, it's important to see hospitalization rates among the vaccinated compared to the unvaccinated population. The figure on the left shows hospitalization rates among 18- to 49-year-olds. The middle is 50- to 64-year-olds, and the bottom is 65 and over. Note for each of the graphics the scale on the X-axis is different. The green line at the bottom of each figure is the hospitalization rate among the fully vaccinated individuals.

And the blue line is the hospitalization rate among those unvaccinated. Among adults 65 and over the incidence was 13x higher in unvaccinated and for those

less than 65 the hospitalization rates were 22 to 23x higher in unvaccinated individuals. This slide shows the variant proportions among the sequenced lineages. The blue color on this figure represents the Alpha variant, and the orange color represents the Delta variant. You can see for recent weeks Delta represents around 99 percent of sequenced lineages.

As booster doses of COVID vaccines would only apply to those who have already received a primary series, I can highlight COVID vaccines already administered. So to date, there have been over 380 million vaccine doses administered in the U.S. The left shows the number of people fully vaccinated by vaccine series type, and on the right is the percent of fully vaccinated population by age. 63 percent of those 12 and over, 65 percent of those 18 and over, and over 82 percent of those 65 and over are fully vaccinated.

So this figure shows the daily trends in doses administered over time. We hit a peak of around three to four million doses delivered per day in the spring,

with a decline in the summer. However, the average number of doses administered has increased since mid-July. This slide shows the proportion of the population receiving at least one dose. Among older adults, in purple, those 65 and older at the top, 90 percent or more have received at least one dose. And among younger adults and adolescents, in yellow, around 50 to 60 percent have received at least one dose.

So now to move to COVID VE estimates. First, we'll look at data available over time. I want to highlight some recent publications that we're pulling data from listed here. This slide shows the VE estimates against hospitalization from studies listed on the previous slide. You can see VE estimates have remained high over time. This slide shows VE estimates against infection over time. We've seen some decreases in VE estimates for the last one to two months. There are a variety of reasons where we can be noting this decline. One aspect could be waning of immunity due to time since primary series.

However, there is another factor to consider

as well. As we've described previously since earlier this year, we have noticed increases of the Delta variant. In late May, Delta was around 7 percent of sequenced isolates, and by mid-July this was up to 94 percent of sequenced isolates. The impact of the Delta variant leads us to this next aspect: what is VE with the Delta variant? This slide shows results of studies that compare pre-Delta versus Delta estimates for VE. Infection or symptomatic disease is on the left, and hospitalization or severe disease is on the right.

In studies comparing pre-Delta and Delta time points, pre-Delta VE estimates are high. VE against infection ranged from 72 to 97 percent and against hospitalization from 84 to 97 percent. Since the introduction of the Delta variant, VE against infection has ranged from 39 to 84 percent, and VE against hospitalization has remained high, from 75 to 95 percent. This figure shows the VE estimates by outcome for the Alpha variants in blue compared to the Delta variants in orange.

The outcomes range along the top, VE for any

infection on the left, symptomatic infection in the middle, and hospitalization or severe disease on the right. You can see that among global studies assessing infections with Alpha versus Delta there was a mild decrease in Delta VE. This may be due to a variety of factors that can impact these results and variation by country, including differences in study methods, different intervals between doses, and timing with vaccination and the variant increases.

This is a summary of VE estimates since the introduction of the Delta variant. The colors correspond to the vaccines assessed in the study. This highlights that, regardless of the vaccines evaluated, all vaccines have remained effective in preventing hospitalization and severe disease but may be less effective in preventing infection or mild illness recently. The reasons for this lower effectiveness likely include both waning over time and the Delta variant.

The next to address VE for older adults. This slide shows unpublished COVID-NET data with VE against

COVID-19 associated hospitalization among fully vaccinated patients 18 years of age and over by age group and month.

COVID-NET conducts hospitalization surveillance with 14 states representing around 10 percent of the U.S. population. Patients must be a resident of the surveillance area and have a positive SARS-CoV-2 test within 14 days prior to or during the hospitalization. Chart reviews are conducted. Data presented at last month's ACIP meeting showed a lower VE in those 75 years and over. However, we're constantly getting updates to the data with backfill for previous months. With these updates, the COVID-NET data through July now show that the VE against hospitalization in adults 75 and over remains over 88 percent. While the VE for this oldest age group has consistently been slightly lower than the other age groups, it has remained quite high and generally stable for the last several months.

So then this slide shows data from the VISION (phonetic) platform evaluating VE against

hospitalization, as well as urgent care or ED visits. VE against both outcomes was consistent, at least 82 percent or higher through at least 16 weeks after the second dose.

Note this data is through June of 2021 and may not represent a full picture with VE with the Delta variant. This study highlights VE for symptomatic infection with the Pfizer vaccine with several of the recent areas of concern. Adults 60 years of age and older are in the light blue. VE against symptomatic infection in adults 60 and over is high, but some decreases are noted against variants of concern. However, it's important to note that these differences were not significantly different.

There were small numbers and very wide confidence intervals for several of these variants. These figures show VE by age and time since vaccination. Infection is on the left, and severe disease is on the right. Adults 60 and over are in light blue. Effectiveness against infection with over 60 percent in the first five to nine weeks after

vaccination with a gradual decline. Protection against severe disease has remained stable, with a decline noted in those 60 and over after 25 weeks. However, also note the very wide confidence intervals for these later estimates.

This slide highlights VE against hospitalization by time since vaccination in adults 65 years of age and over. VE has decreased slightly over time but remained high and, again, differences by time intervals since vaccination were not significantly different. So next we can consider long-term care facility residents. There was some question initially for how these older potentially medically frail adults may respond to the vaccine at all. However, this shows that initially VE against infection was 74 percent or higher by vaccine.

However, as we look over time, moving into the recent months where Delta was the primary variant, VE against infection has fallen to just over 50 percent. So then this is the same summary slide as before, but the other ages are grayed out. And we've added the

estimates for adults 60 years of age and over to put these estimates for older adults into the overall context. Lower VE against infection was seen for older adults, particularly the long-term care facility residents. Follow-up is needed to monitor these VE results over time.

So in summary, COVID vaccines continue to maintain high protection against severe disease, hospitalization and death. Protection against infection, which includes asymptomatic or mild infections, are lower in recent months. However, it's difficult to distinguish the effects of increased time since primary series versus the impact of the Delta variant. It's important to monitor trends of effectiveness by severity of disease over time.

I want to thank the team of people that have helped pull this together, our ACIP team, and the entire vaccine effectiveness team at CDC. I'll highlight that the next two slides contain references that were listed. And I'm happy to take questions. Thanks.

DR. ARNOLD MONTO: Thank you so much, Dr. Oliver. And thank you for keeping us to time. We do have time for a few questions before we move on to the next presentation. Dr. Gans.

DR. HAYLEY GANS: Thank you, Dr. Oliver. That was very helpful. I'm wondering if you could elaborate a little bit more because they seemed to be lumped by Pfizer/Moderna in the breakthrough disease. Can you elaborate more since we're thinking about Pfizer at the moment -- application. Can you give us more information about breakthrough disease and how it relates just to the Pfizer vaccine? Were the large majority of those Pfizer versus Moderna?

DR. SARA OLIVER: Some of that has to do with the study platform. Several of them don't have the power to split apart individual vaccines and still get stable estimates, so many of them had to lump mRNA vaccines together. There were some and a few of the slides did look at if you compared -- like we had estimates for Pfizer and Moderna that are in there. But many of the platforms had to kind of lump the mRNA

vaccines prior receipts together. I will say that the Vision platform is one of the larger ones, and it has been able to obtain product-specific estimates. And so I can share those platforms -- the estimates with you.

I think compared to -- the Pfizer estimates were slightly lower than the Moderna estimates, but we'd have to kind of monitor that over time and look at it across various platforms.

DR. ARNOLD MONTO: Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Thank you, Dr. Oliver. Thank you for your presentation. My question is with regard to mitigation measures in addition to vaccination. Obviously, these have an impact on risk of exposure, and I was curious whether any of these studies address those measures and the impact they might have?

DR. SARA OLIVER: Yes, it's difficult if you kind of overlay a lot on the time. We know that sometime, as Delta was taking over, there were also changes in how we were doing some of our distancing and non-pharmaceutical interventions. I know several of

the studies have attempted to look at this. Unfortunately, it's really difficult to get behavioral interventions and data on masks and behaviors in this, so we'll continue to attempt to measure. But I know it's been difficult for each of the platforms.

DR. ARCHANA CHATTERJEE: Thank you.

DR. ARNOLD MONTO: Dr. Kurilla. One more question after Dr. Kurilla before moving on.

DR. MICHAEL KURILLA: Thank you, Arnold. Sara, it's convenient to divvy up the population into vaccinated and unvaccinated, but there actually is a subgroup that is unvaccinated but prime infection and that has been increasing over time. And failure to account for that would seem to actually underestimate vaccine efficacy going forward. So I'm wondering, have you attempted to take that into account in terms of actual calculation of vaccine efficacy?

DR. SARA OLIVER: I know that the platform -- many of our broader, more robust platforms do a test-negative design, but they're not able to do serology screening on everybody who would be admitted. So I

don't know that included into the specific -- they're not, like, screening for serology prior to including unvaccinated individuals. But I know that several of the platforms -- Vision, Ivy (phonetic) -- attempt to account for this with their statistical analysis.

DR. MICHAEL KURILLA: Okay. But you haven't done any attempts at bounding what that given overall zero prevalence estimates are? You haven't done any bounding of how that may be impacting calculations of overall vaccine efficacy?

DR. SARA OLIVER: I'll tell you I can get back -- I can check with specific site PI's and get back to you potentially this afternoon around exactly how their analyses have adjusted for that.

DR. ARNOLD MONTO: Right. Dr. Meissner, final question. You're muted.

DR. CODY MEISSNER: Okay. My question is the charts and tables you showed us -- some were for adults over 75. Some of the data were for adults over 65, and some were for adults over 60. How do you pull that -- I mean, they're fairly discreet groups in terms of the

interval of time since they received a vaccine, for example. How do you break down the risk in those different age groups?

DR. SARA OLIVER: Yeah, so essentially what we reported is what has been published and was out there, so several of the studies we had to take -- especially the ones not conducted at CDC -- we had to take the interval and age as they reported them. There is absolutely a difference by age group, and so in some of the platforms where we have more people and could get stable estimates -- so COVID-NET is a larger system, so we tried to break out that 65 to 74 and 75 and over.

Many of the platforms, though, that have smaller numbers just aren't able to get that granular. So that's why some of the platforms reported 65 and over with an acknowledgment that they're likely is an age gradient. And I mean, a 65-year-old may not be exactly the same as an 85-year-old, but we can't necessarily report stable VE estimates for each individual age group.

DR. MEISSNER: Thank you.

REAL-WORLD EFFECTIVENESS OF COVID-19 VACCINES

DR. ARNOLD MONTO: Okay. Thank you, Dr. Oliver. And as I'm going to mention to all of our speakers, we may well have more general questions later on, and I hope you can stay around with us during the entire day. Next, we go outside of the U.S. Our next speaker is Dr. Jonathan Sterne -- Professor Sterne who is at Bristol Medical School in the UK.

DR. JONATHAN STERNE: Thanks very much and I'm honored to be asked to present at this important meeting. The title of my talk is "Real-World Effectiveness of COVID-19 Vaccines." These are my declarations. I don't have any financial interests with any of the firms or entities that are related to the meeting topic. I'd like to acknowledge the authors listed here who have diligently assembled data on estimated effects of COVID-19 vaccines that I will present in the early part of my talk.

So, the title of the talk is "Real-World

Effectiveness of Vaccines." And I want to emphasize that randomized trials provide the best estimates of effectiveness of any healthcare intervention in the real world. The issue that makes life difficult in the context of the question that's being addressed by the Committee today, is this host of urgent questions about COVID-19 vaccines have not been addressed in randomized trials. For example, for completely clear reasons, the randomized trials were almost exclusively conducted before the era of the Delta variant.

The ongoing emergency, the amazing success of the vaccines means that we have to make far-reaching policy decisions such as the one being considered today using observational data. But a better title to my talk might be "Estimated Effectiveness of Vaccines in Observational Studies." Given that I'm going to be spending my time talking about the potential bias in these studies, an even better title might even be "Estimated Effectiveness of Vaccines That is Biased by an Unknown Amount and How to Think About Such Biases."

Now, colleagues at the WHO and Cochrane are

running an amazing systematic screening and data extraction process on published studies on vaccine effectiveness, and they are screening hundreds of studies per week, classifying them and published observational studies classified according to whether they're peer-reviewed or are available as a preprint and according to whoever that perspective or retrospective or cross-sectional and according to the underpinning study design. There have been 178 such studies on vaccine effectiveness against variants of concern as you can see here, with a number of different study designs that primarily cohorts and test negative case-control designs, and plenty of studies on the Delta variant, 76 of them.

Among those 76 studies on the Delta variant, there is a legitimacy on vaccine effectiveness and number of studies are increasing weekly. There are 51 cohorts, nine test negative case controls and if we look at the outcomes, the outcomes considered are laboratory concerned COVID, 57 studies, symptomatic confirmed COVID, 34, severe or hospitalized COVID, 37,

and death from COVID, 16.

And Dr. Oliver's talk last time beautifully summarized the data that was out there particularly as it relates to the question being considered by the Committee today. So those data were summarized in a paper in the *Lancet* published by these authors. I was a minor contributor to it, and it has appeared on Monday. That paper summarized efficacy overall according to variant showing as we've seen that efficacy against -- firstly, the efficacy against the rare disease is uniformly higher than efficacy against any infection. And secondly, that the efficacy against Delta seems high and similar to efficacy against Alpha.

In a small number of studies, the efficacy for early versus later follow-up appeared similar for effectiveness against severe disease, although somewhat lower for effectiveness against any infection. This slide, diligently put together by Dr. Anna Maria and Alres Streppo (phonetic) and Professor Sir Richard Peter (phonetic) just yesterday, summarizes the current evidences, as recorded in this dataset in trial of

studies and study results, the efficacy of messenger RNA vaccines against severe disease in settings where the Delta variants is circulating up to this week.

And as described in the previous talk, in most context if you look at the middle column here -- the right two columns show us the confidence interval. Efficacy remains high, and so for example this study in Minnesota where estimated efficacy was a little lower for both the Pfizer and the Moderna vaccine, the confidence interval was rather wide in that study. I won't spend time talking about this slide. The evidence is beautifully summarized in the previous talk.

So I'm going to spend most of my time talking about methodological issues in estimating vaccine efficacy during the rollout. I'm going to give some examples from analyses that a large team of us have been doing in the UK based on the OpenSAFELY analytics platform, and we've been fortunate to establish in the UK near population coverage on detailed linked electronic health record data. And OpenSAFELY provides

a trusted research environment within which those data can be securely accessed and analyzed with appropriate disclosure controls.

Now, I want to emphasize that my examples are from analyses of these data, but they're not there to tell you about the results. They're there to try to illustrate general issues in trying to estimate vaccine effectiveness from observational studies. Here are the issues that I'm going to cover, and the first, and obviously important one, is the problem of confounding. I'll call it baseline confounding for reasons that I hope will become clear. That presence is characteristics in individuals that predict both vaccination and the outcome that we're interested in.

Confounding occurs when there's a common cause of both the vaccination and the outcome event, which might be symptomatic infection or hospitalization with COVID. In that circumstance, the association that we estimate in our observational study may not equal the cause and effectiveness of the vaccine. The reason that we randomize fundamentally is that randomization

should remove confounding in a high-quality randomized trial by removing the link between prognostic factors -- factors that influence the outcome -- and vaccination because only the player chance determines if someone's vaccinated.

Now, here's a graph of the rollout of vaccination in England from OpenSAFELY in the over 80s in the open panel that started on the 8th of December 2020 and rather later in 70s and 79-year-olds which started in January. Here vaccination with Oxford/AstraZeneca is in green. Vaccination with Pfizer/BioNTech is in purple, and you can see what characteristic of countries that achieved rapid rollout with high takeup is that we see rapidly we get to a point where very high proportions of the population have been vaccinated.

The light purple here is the receipt of the second dose of Pfizer-BioNTech, and that happened for only some people vaccinated with Pfizer and almost nobody vaccinated with AstraZeneca because the UK changed its vaccination schedule to 12 from 3 weeks

early in January 2020. When we look at this we can ask, "Well, what predicts the speed of takeup, speed of being vaccinated? What factors predict being vaccinated faster rather than slower?" That's what's shown on the next slide here which shows estimated hazard ratios for people aged 80 years and over in the left two columns of figures and people aged 79 years in the right two columns of figures, separately for Pfizer and BAT16 to B2, for Oxford/AstraZeneca, ChAdOx1.

I'll just highlight a few results. This is just to show you that patient characteristics that predict occurrence of COVID outcomes also predict whether you get vaccinated, even in a situation of rapid rollout in publicly funded healthcare such as in the UK. Even within these age groups, age influenced whether you got vaccinated and not necessarily in the same direction or consistently for the two vaccines because it's dependent on logistical issues.

Even in the context of this publicly funded healthcare system, less deprived people in group five were vaccinating faster than more deprived people in

group one, and that was true for both vaccines and both age groups. It's well documented that vaccine hesitancy is related to ethnicity in the UK and in other countries, and, sure enough, white people got vaccinated faster than people of other ethnicities. People with learning disabilities got vaccinated slower, and previous vaccination, which may be related to underlying healthcare behaviors or vaccine hesitancy -- so people who'd received flu vaccines in the previous years may also be related to comorbidities were more likely to be vaccinated with the COVID-19 vaccine.

So there is evidence to think that estimates of vaccine efficacy will be subjected by astute confounding. One way to address that is to adopt a test-negative design in which we don't look at the whole population, we compare individuals with symptoms who test positive, the cases, with individuals with symptoms who test negative, the controls. Now, that may reduce confounding, but as it's been well documented -- and here's a pair of papers in the

American Journal of Epidemiology published in 2016 discussing test-negative design in the context of flu vaccination. And there is no reason to think by just doing a test-negative design you will remove confounding, and there are various consequences of test-negative design that are discussed in detail in those papers. But I think within the context of COVID-19 vaccination careful evaluation of the potential for bias in estimates of vaccine effectiveness from test-negative design seems warranted and indeed urgent.

Back to my graph of the cumulative incidence over time because it tells us the next problem we have when we try to estimate vaccine effectiveness, which is that if I take somebody who is unvaccinated on particular dates, for example, the 15th of January 2020 and that person, although they're unvaccinated and they may serve as a comparator at that moment in time, is also likely rapidly to become vaccinated. And that gives us a problem in choosing a comparison group for our estimates in vaccine effectiveness.

Because of the very rapid rollout of

vaccination, unvaccinated people rapidly become vaccinated, and there's a solution to that which seems pretty obvious, which is to split the rollout time for each individual in our population into time unvaccinated and time post-vaccination among the large majority of people who ultimately are vaccinated. The difficulty is that that gives us a new problem that hasn't been extensively dealt with in studies of vaccine effectiveness, which is the problem of time-varying confounding.

So I've discussed already how patient characteristics at the start of follow-up may be confounded because they predict both vaccination and COVID-19 outcomes. But as we move through follow-up and people get vaccinated, there might also be confounding after baseline by time-varying factors, and we call those time-varying confounders. Here are some -- a difficulty here is that specialty methods such as, although not exclusively marginal structural models, are likely to be needed when there are time-varying confounders.

So here is further analysis from the same data set that showed you earlier looking at time-varying characteristics predicting vaccination in those two age groups in England. You can see that people who had recently tested positive for SARS-CoV-2 were hugely, at least 90 percent, less likely to be vaccinated. In fact, there was almost nobody was vaccinated within a week of testing positive for SARS-CoV-2. So that -- and clearly that's a confounder for being hospitalized with COVID. So there's every reason to think time-varying confounding is also a problem here.

Why is it such a difficult problem analytically? Well, because it's a confounder, because having a positive test predicts when you get vaccinated and also predicts whether you're hospitalized with COVID, but it's also on the causal pathway from being vaccinated to being hospitalized. That means that using standard modeling strategies may not work. We tried to do analyses using marginal structural models to overcome this problem, and these are the results. And I'll quickly take you through them.

So the colors here relate to the degree of the adjustment. In green, we have basically just region adjusted but no further adjustment. In orange, we have adjustment for just baseline confounders, and in blue we have additional adjustment for the time-varying confounders. The left-hand graph is any vaccine, and the right-hand graph is Pfizer only. The upper sets of graphs is the outcome positive tests, the middle set of graphs is COVID-19 hospitalization, and the bottom set of graphs is all cause mortality.

Firstly, you can see that adjusting to the time-varying confounders makes a big difference and attenuates the apparent effect of the vaccines on all cause mortality. It has some effect, although less dramatic, on the other two outcomes. You can see -- and this has been seen in a number of studies that there is completely implausible protection immediately after vaccination, even when we adjust for the time-varying confounders. And I think that's just (audio skip) confounding, and I'll say a bit more about that in a moment.

So the difficulty we have is that even with these details, electronic health records and using probably the best method available and controlling for wide -- for an extensive set of confounders, we get implausible levels of protection. Why implausible? Well, firstly they weren't seen in the trials, and secondly, I think it will be broadly agreed that we don't expect huge protection against all cause mortality or hospitalization within a week of vaccination and with the first dose only.

So what we like to do is we like to hope that, that bias which I think it's plausible bias that we see very soon after vaccination goes away but what we see later are good estimates of vaccine effectiveness. The worry we have is that, well, if it's biased early, we don't know when that bias goes away. But I think we should be particularly concerned about short follow-up after vaccination for the reasons I've explained. We get similar results for the 70 to 79-year-olds. So I think there may be a problem with the unmeasured confounding, particularly soon after vaccination.

One plausible explanation is that if you show up to vaccination in the UK, there's a big sign saying, "Please go away if you have symptoms of COVID." So, people are likely to delay their vaccination if they have symptoms, and that's not recorded anywhere in the healthcare record unless they subsequently test positive or show up for healthcare. Of course, that makes symptoms a time-varying confounder, but it is not measured. So bias because recent symptoms predict postponement of vaccination may wane with time, but it seems particularly hard to estimate short term effects in vaccination.

Another couple of important issues. Firstly, it's vital to account for the fact the incidence of the outcome vary so dramatically over time. Here's the incidence of hospitalization in the last six months in the United States readily available on the web, and you can see that you don't want to be comparing somebody on the 31st of August with somebody else on the 31st of July because things change so rapidly. So we have to deal with time since vaccination as one aspect of our

analysis. But it's vital that we also deal with calendar time in our analysis, and people do that in a variety of different ways.

The way that diversity makes the studies hard to appraise, but it will usually be important to carefully allow for both calendar time and time since vaccination in analysis. Finally, a word about persistently unvaccinated individuals. This is the other end because we're most interested in people who've been vaccinated for some time and whether vaccination effectiveness is waning, and in many highly vaccinated populations, perhaps less so in the US. That means we're dealing with a highly selective set of individuals whose characteristics we need to understand.

We are particularly concerned, raised in a question before my talk, is what proportion of those remain unvaccinated because of recent infection that conferred protection? So it's hard to estimate vaccine effectiveness, and we need careful and critical evaluations. Here's my final slide, and I will skip

through because I'm out of time. We need to think carefully about confounding. We need to think about how our analyses need to allow for all stages of the rollout. We need to control for a wide range of potential confounders.

In studies of long-term vaccination, we need to ask about what proportion of the unvaccinated are protected because of previous infection. We need critical appraisal of test-negative designs. We should be very cautious of comparing short-term benefits of vaccination because of the potential of imaginative confounding, for instance delay to vaccination. We need to deal with rapidly changing incidence of outcome events. Finally, ideally there should be an analysis plan published before outcome data were available to reassure us that data weren't cherry-picked.

Thank you for your attention.

DR. ARNOLD MONTO: Thank you so much, Professor Sterne. As someone who does test negative designs and knows the strengths and weaknesses of that design, I think you've covered it brilliantly. My

first question, because we're going to be confronted with an issue of U.S. data versus outside the U.S. data, how did you handle the fact that with the mRNA vaccine -- the Pfizer-BioNTech vaccine in the UK -- many people did not get the second dose in exactly three weeks, which was the protocol in the U.S.? But the dose was delayed, and therefore the immune response might be different.

DR. JONATHAN STERNE: So, the short answer is we didn't because the analyses I showed you looked at first dose and didn't account in any way. There are some incredibly interesting data coming soon, I believe, in press from the ONS Community Infection Survey that will speak to exactly that issue and may indeed suggest the UK made a good call in extending the time between first and second doses.

DR. ARNOLD MONTO: Right, that's exactly what I'm referring to. Dr. Kurilla.

DR. MICHAEL KURILLA: Thank you. I don't know why my camera is not working. You highlighted the issue --

DR. ARNOLD MONTO: Can still hear you.

DR. MICHAEL KURILLA: Yeah. Okay. Good. Thank you. You highlighted the issue in seeing an effect in the immediate post-vaccination period that would not be expected due to the effect of the vaccine, but I'm wondering do you think there could be potential for an antigen-independent vaccination enhancement in some degree of immunity and in shorter term that period of time that that will wane very quickly -- that that may actually be overestimating short term estimates of vaccine efficacy that would then change over time?

DR. JONATHAN STERNE: So, it's possible. I mean, the difficulty for the Committee is that you're making incredibly important policy decisions very rapidly in a situation of uncertainty, and there are very good reasons those decisions have to be made. I do think that we can look to the trials for good unconfounded suggestions of the likely short-term efficacy.

DR. ARNOLD MONTO: Dr. Gans.

DR. HAYLEY GANS: Thank you for elaborating

some of the things that we've all been very concerned about in a very organized way. I'm wondering when you apply all of the confounders and all of the considerations that you've made, what are the studies that filter out at the end that you would highlight for the Committee that would actually suggest that we have good unbiased or at the best that we have in terms of how we should be (audio skip) vaccine (audio skip)?

DR. JONATHAN STERNE: So I'm not going to identify individual studies, but I tried to on my last slide identify characteristics. And they would include careful control for the confounders that we know are really important, such as age of vaccination, availability of vaccination, as precise as possible and then if possible also other characteristics and details health record and extremely close matching for calendar time so that broadly speaking somebody who experiences an event should only be compared with somebody who's being followed up on the same day. And it's perfectly possible to do that setting up your survival analysis in the right way. But I'm not sure that all studies

have done it. But, I mean, I sympathize with you because I find it incredibly hard to look at the very diverse set of descriptions on what's been done in the individual studies and to know, well, did they do the things that I've just talked about?

BOOSTER PROTECTION AGAINST CONFIRMED INFECTIONS AND SEVERE DISEASE – DATA FROM ISRAEL

DR. ARNOLD MONTO: Thank you so much, Professor Sterne, and again, we appreciate your keeping to time because we have a very busy day. Now we move to looking at booster protection against confirmed infection and severe disease data from Israel. We're going to hear two speakers who will speak one after the other, and then we will have the question period first. And I'll introduce both right now. Sharon Alroy-Preis, who is the Director of Public Health Service at the Ministry of Health in Jerusalem, Israel, and then, Professor Ron Milo, who is at the Weizmann Institute in Israel. Dr. Alroy-Preis, please.

DR. SHARON ALROY-PREIS: Dear Chairman and honorable Committee members -- the Israel Ministry of Health, we were asked by the FDA to present our data on waning and booster effects, and we are delighted to do so. It's important for us to start by emphasizing that we do not pretend to tell other authorities what to do in their setting. We're here to present the data from Israel and the decisions that we came up with in our setting, and we hope that this will help other countries or enable them, other authorities, to reach their decisions with the most advanced latest evidence that we have in Israel.

Based on the multiple logos that you see on the screen, I would like to highlight that the work presented here was done by several leading academic institutions in Israel in collaboration. Knowing that the evaluation of the booster dose would be critical to Israel and the rest of the world, the analysis was done with extreme caution by different analysts from different institutions by different analysis methods, as Ron will describe. And I would like to thank all

these institutions coming together to do this work very diligently for several months.

So we are both presenting, Ron and myself, and we have no competing financial interests to disclose. I would like to say that Israel Ministry of Health and Pfizer have data-sharing agreement on public health surveillance data. However, since the data that we are showing here was actually done by these academic institutions, only the final results were shared with Pfizer. So I would like to take you back in time to December 2020 in Israel. We started to see a surge in cases, our third wave, and this was actually after having two waves and two lockdowns.

And when we were at the exit from the second wave, we had really pandemic fatigue in the country, and so we saw once we started opening the economy we weren't even able to open everything up. As we were starting to open places, we saw an increase in cases, both confirmed cases but also severe and critically ill. And there was a significant burden on the hospitals at that point in time. We decided on a

lockdown, but as I said, that decisions was not as -- the compliance of the public was not as it was in the previous two waves.

Thankfully, we had the ability to start a vaccination campaign in December, so Israel started vaccinating as soon as there was FDA approval for the Pfizer-BioNTech vaccine. And there was a quick compliance and uptake of the vaccine. We opened it in steps based on ages, and we reached a very high level of vaccine. And with that, the vaccine uptake, we started to see a decrease in cases, over 100 fold decrease in cases following the vaccination campaign. And as I said it was a partially effective lockdown at the time, and the main thing was that, when we opened the lockdown, we were able to open everything up -- lift all the restrictions step by step. And the cases did not go up again.

We saw and also the fact that we had reached high level of population-wide immunity early on, which was wonderful -- but we also can see that we're basically three months ahead from other countries when

we're talking about now waning. So the very efficient vaccination campaign made Israel the leading country, but when we compare it to other countries, there is a time gap. So Israel reached about 40 percent of the population covered roughly three months ahead of other countries that have five million citizens or more.

And that is important when we move ahead to explain why our data may be different than other settings. Before we move ahead, it's worth noting several things about Israel. First, all the residents are covered by four HMOs with comprehensive electronic medical records. The second point is that we have large PCR testing capability in Israel, so we are basing all of our data on PCR and not really rapid antigen testing. Two things that are allowing us to really monitor the effects of policy changes is that every COVID-19 test result, positive or negative, is reported online to the Ministry of Health, so we know every day how many people are tested positive and negative.

And all vaccines given in Israel are reported

online to the Ministry of Health. So our capability of doing really online vaccine effectiveness is comprehensive. So our third wave was mainly Alpha variant as you see, and we started sequencing Delta variant sometime at the end of March. But it was really rare. It was among people traveling abroad, and it was one at a time. But there was steep increase in Delta isolation, reaching over 98 percent of the cases in June.

And at the same time, we started to see our fourth wave. We are now still in our fourth wave, experiencing the highest level of infection that we have seen so far in this pandemic, and this is despite widespread, over 60 percent, of doubly vaccinated individuals and in the vulnerable population over 85 percent that are doubly vaccinated. And once we saw that, we're trying to figure out what that tells us. We saw daily cases rose by more than tenfold in a month and a half, so from roughly 12 cases a day to about a thousand in a month and a half, and what was more worrisome is that we saw severe active cases increase

by more than tenfold in a month.

Among them was 60 percent vaccinated individuals, fully vaccinated individuals, so at that point, we had to stop and ask the question exactly as the CDC officer said. Is that a Delta issue, or is that a waning immunity issue? We had some clue that it may not be the delta variant, at least not alone with its effect, because we started vaccinating 12 to 15 years old with FDA approval. And they actually had a fresh vaccine, and amongst them, we saw vaccine effectiveness of around 90 percent.

So the majority of them were protected, but still, you can't really say because of the age difference and everything. The other question we needed to figure out was what about the waning, and does that play a role? And as Ron will describe now the analysis, we did we think this is a major part of our (audio skip).

DR. RON MILO: Okay. So good morning, everyone. What I'll be showing you are the results of the observation analysis that we did in Israel, which

is after relatively short time since the vaccination campaign. In spite of the potential biases, as we described in the two papers regarding the VE analysis, as well as the relatively short follow-up time. We thought it was our responsibility to analyze the data as thoroughly as we could and share it with the world through peer review. And this is what I'll be presenting today.

So this is a bit of a heavy slide, a complicated slide. It'll be great if I also get a cursor at the bottom, but I would say let's try and follow in the following way. Let's start from the X-axis. You can see three cohorts, and we'll be focusing initially on the column on the right, ages 60 and above. On the Y-axis, you'll see the confirmed infection rate per 1,000. We'll be talking about rate of SARS-CoV-2 confirmed infection, which is both symptomatic and asymptomatic based on PCR results.

I'll be talking here about people that were confirmed in the month of July, so as Sharon was saying, this is vastly dominated by the Delta variant.

And the different shades that you see here refers to what happens for people that were vaccinated at different times, starting from the dark colors would be generally the ones that's vaccinated early in the campaign. Okay. Great. I've got a cursor. Good. So you can see here this is at the beginning, and then you can see we're proceeding here based on the month of vaccination from six months prior to the study period up to two or three months from the study period.

I think you can see that there is a change in the rate of confirmed infections per 1,000 people. And this is in both of the ages, 60 and above, which is what you see here. And you can also view what happened to the other age groups. The other age groups, I do want to mention we see the ones that are vaccinated earliest tend to be healthcare workers or people at risk for most of the severely immunodeficient people, and therefore they should be cautious. But you can see a signal waning in both other cohorts, which we interpret as the waning effect.

You can also see here what happens in terms of

waning immunities in the relation to severe disease in the ages 60 and above. The Y-axis is again regarding the range of 1,000 individuals in the study period in the month of July. All of those -- or 99 or whatever percent have the Delta variant because this is, by far, the most dominant. You can see the confidence intervals is 95 percent confidence intervals. We can see that they are large enough. This is because the number of cases is smaller. I would mention that we have here over a million people that are being analyzed, so I would say it's not easy to get very small confidence intervals for these studies even though the study group is very, very large.

And you can see the change in rates through time. All of this, by the way, is publicly available. We made it available on the archives, and it's in the final stages of being published. Here we have to also present what's happening in the younger age groups. This is mostly preliminary data, so you can see the ages 50 to 59, 40 to 49, and the younger age groups. The numbers are much smaller because the rate of severe

disease is smaller, and therefore the statistical confidence is also not as strong.

And one can see the general potential trend, but it is hard to conclusively interpret it given the relatively small numbers. We do see what can be indications of a trend, but it depends heavily on how you want to also interpret what happens with the medical healthcare workers that were vaccinated in the month of January. There is an important point here that I want to mention that was an issue in Israel when trying to think about this. We saw in the CDC presentation and the following presentation they were mentioning the issue of high degree of protection that you get from the vaccine for severe cases.

I want to just take a minute to show something that I found that was completely confusing in the discussion for us. There's no doubt that the vaccine gives good protection, meaning much better than not having the vaccine, and this has been shown in many different ways. And we observe it as well. At the same time, you can have high protection of 97 percent,

or you can high protection of 85 percent. So 97 percent is what has been published, is what is observed for, again, severe disease. 85 percent was mentioned in some of the previous slides and also concurs with what we seem to be seeing right now with Delta for those who are vaccinated relatively early, meaning half a year ago.

And while 85 percent might still seem very high -- this is only a 12 percentage point difference -- I just want to point out that this translates -- the 97 percent vaccine efficacy, it means 3 percent relative risk; whereas 85 percent vaccine efficacy means 15 percent relative risk, meaning fivefold increase in relative risk, which is a very large increase, a full change in the number of severe cases vaccinated -- doubly vaccinated severe cases which has to be taken care of in an (inaudible) system. And this is in line with the value that Sharon was mentioning on what we saw with the sharp decrease over half of the unvaccinated people.

Based on the evidence of waning in Israel and

the trajectory towards exceeding national vaccination capacity (inaudible) severe cases, Israel started to begin a third vaccination campaign on July 30th starting with the elderly. I want to show you what we found regarding the effect of those dosed. Here is just the outline of the temporal campaign. As I said we started the end of July/beginning of August, and there's been about one million doses given for ages 60 and above. And you can see also the other cohorts started with the 60 plus two weeks later and then 40 plus, et cetera.

All together we're close to three million booster doses which were given to date. You can see here is a fraction of the eligible population in each cohort. The eligible are the ones that got two vaccines. They're eligible to take the third vaccine assuming it's over five months in our case, and you can see there's a significant faction of the population. So you can see it started mostly with the elderly, and that's made us do the analysis for this age cohort, which is where we have the most follow-up time.

You can also see here the fractions of those eligible that were vaccinated with a third dose to date. Overall we're talking over the age of 60 plus that were included in the study. We're talking about a million people all together. We saw about 30,000 confirmed infections of the period in August. We are still in the period of a wave and therefore a lot of cases. Okay. Just before I get to the results, let me show you what we might be expecting or the full result I'll be showing you. On X-axis I'll show you the day for vaccination, and on the Y-axis, I'll show you the full reduction in risk compared to two doses.

So throughout the study, for many reasons, for example that were mentioned in the previous presentation, we're sure to compare between those with already two doses and those who have decided to also take the third dose and compare between those two groups and not the unvaccinated, which might contain some potential confounders. In the beginning, as was mentioned before, there could be also possible trend in biases in the days just following the third dose.

People usually -- we see the signal. There's a tendency to go and do less PCR tests for COVID-19.

But then we see that's decreasing, and then we're looking at the time period of about 12 days onward, which is the time scale in which we're expecting to see the effects because of two reasons. One is because we know that there's time until the neutralizing antibody response increases. That's usually another few days or a week. Then there's also the time between whenever you're infected or get the protection from infection and the time that this is observed through a test in PCR.

The average in Israel is about five days, probably related to the incubation period of developing symptoms or just in general also when you look at (inaudible) et cetera. That's roughly seven days or five days or 12 days exactly where you're expecting to see the effect being observed. So here are the results. Again, this is on the X-axis you can see the size possible infection, and on the Y axis, you can see -- actually, yeah. Sorry. On the Y-axis you can see

the full reduction of the rate, again, compared to the two doses. All of this will also be publicly available and now is -- we gave the slides requested three days ago. By now so publish in *Israel Journal of Medicine*.

All the results I've just shown you are based on performed regression in order to take into account as many of the confounders as we could. It's adjusted for age, for gender, for demographic group, for the time in which the second dose was given and the calendar date. Just as it was mentioned before, these two temporal effects should be taken into account. And we'll be comparing -- when we're talking about protection from the main analysis, we're comparing between what's happening in 12 days onward.

This is what happened with no booster, meaning only two doses. Here is a summary of the results. We gained an estimated protection of about elevenfold. You can see the confidence levels here are relatively small, 10 and 12, as a results of many risk-based going to develop this. And the second is over 1,000 infections in this group over those 10 million risk

base and about 5,000 infections or 4,000 infections in the two-dose only, no booster group.

The rate difference is about 86.6 per 100,000 person base. This is the results for the age 60 and above. We also have preliminary results of the ages 50 to 59, and we can see a consistent picture where after about 12 days we're seeing about this tenfold protection. Similarly, for the ages 40 to 49, we see again something like a tenfold decrease -- tenfold protection, again, doing it at the same time of a full regression adjusted for all of those aspects. We understand the importance of doing this analysis as thoroughly as possible, and therefore we tried to use different approaches.

So what I showed you so far is based on the performed regression approach. We also used a matching approach, which is common in many of the studies for doing this, and when we're doing matching between those who got three doses to two doses, we got a very similar results in terms of the reduction and the risk. We also did another kind of analysis being worried this

may be (inaudible) we should account for just in terms of the behavior for the fact it takes three doses versus two doses. And therefore we only took those who took three doses.

And as you can see here, we compared between those that were 12 days onward versus now the control group who would be people decided to take the third dose but in looking at what's happened to them four to six days following the booster dose. We think that even under this analysis -- we think that we're getting about fivefold reduction meaning a significant protection also in this more stringent or conservative type of analysis. Let me move on to show you what we get for the severe results. Here you see what happens to the age 60 and above, the severe COVID-19 for the same study period.

We've seen, again, a very significant decrease in the rate on the order of tenfold or higher and an (inaudible) difference of 7.5 severe cases per 100,000 person base. Going back to the issue of Delta versus Alpha and waning, I want to point out that overall what

we're seeing is we have the -- in terms of the confirmed infection, if after waning is something on the order 50 percent versus the Delta which is also what we observed in these studies from around the world. With a tenfold increase, which is roughly what we're seeing, you get back to about 95 percent.

Similarly, if you sub for about 80 percent vaccine efficacy against severe disease, with a tenfold increase we get to about 97 percent or higher. And these are similar to the reports of what's happened in terms of protection against the Alpha variant with a first vaccine. So overall it seems like with a booster dose we are getting, again, the protection we originally got against the Alpha variant. I want to point out that it's very hard to decompose whether the net effects only come from the waning or only comes from the difference between the Alpha and the Delta.

What I've shown you enabled us to do some of that, but overall I'd say even if you can't decompose exactly the effect, what we're seeing here is that in totality the combination of both gives us the results

that I've just presented. I want to finish by just saying what happens at the national level. This is what the reproduction numbers are as we observed in Israel, and as you can see throughout the month of June and even before that, we were at about 1.3 to 1.4, which translates to a doubling every 10 days, which relates to what Sharon will say that we had over 100-fold increase in the prevalence.

This is what's happened in the following weeks and months. We tried to reinstate the green passport, but that did not have the marked effect on the reproduction number. Then with the booster contained with the delay, this is roughly in line with what we expect. We started to see the continued decrease in the reproduction number. You can see that this took a while, and therefore we had to make a decision also for the other age groups where we still had an increase in the numbers and the R was still above 1.

This shows you, again, the effectiveness at the national level. What you're seeing here is the function of time and also what happened to the number

of new daily cases in terms of confirmations following the administration of the booster dose. This was for the ages 60 and above, and we see the sense of delay of about two weeks. We're seeing a decrease. Whereas for the other ages where the booster dose was still not administered, we see a continuous rise. This is in terms of confirmation (inaudible) in terms of what happens in severe disease.

So we're talking about daily severe cases. You can see the booster dose being administered, and you see between the delay, you start to see a sharp decrease for those vaccinated versus those that were unvaccinated in which the rise continued and did not go down significantly. Okay, Sharon. Sharon, you're on mute.

DR. SHARON ALROY-PREIS: Thank you. You can see here the projection that we were looking at. The pink projection was based on no booster at all and looking at the reproduction numbers as Ron said we were doubling every 10 days. And we got to places of thousands of cases doubling every 10 days. It is scary

and the fact that we had roughly 1.5 percent of those confirmed cases turning into severe and critically ill patients. So you see here the pink line, which is the model we're looking at. That was based on the reproductive number, the number of confirmed cases that we had each day, and then how many of them would turn into being severe cases and then accumulating them over time. And you see the purple one looking at a model taking into consideration a booster dose with 80 percent compliance rate.

The black line is actually the line of our data. So if we only looked at the model at the end of August, if we had not started booster doses at the end of July, we would have come to the capacity of Israel hospitalization capabilities and probably have gone beyond it. So 2,000 severe cases that are hospitalized in hospitals in Israel is way beyond what we experienced in the third wave. Just to give it context, we were at 1,200 cases, and it was stretching. We had increasing mortality rate. It was a stretch.

So this we were anticipating at the end of

August 2,000 cases -- active severe cases a day in the hospitalized. So what happened is the booster dose we were able to dampen that effect, and our severe cases now that are hospitalized are roughly 700 or less. And that has stayed stable even though we still have days of 10,000 confirmed cases a day. The other point, except for effectiveness and what we think is important to see with the vaccine, the other really important point is the safety. So I'm going to show you a few slides of the rate of events that are reported to the Israel Ministry of Health.

I want to emphasize from the get-go that we are sure to have under-reporting probably the same at every dose, but if we have more under-reporting of the third dose we still would think that serious adverse events would be reported to us. And I will touch on myocarditis in a moment. But this is generally the adverse events reporting to us from the first dose, the second dose, and now the third dose. What we can clearly see is that for systemic adverse events we didn't see any new types of adverse events, and the

rate, to be modest, is at least the same if not lower. And if we look at local adverse events, we would still see the same trend.

We don't see any new adverse event. We know that there's more lymphadenopathy, but we're not seeing any new adverse events. And the rate is smaller. Again, I say that with caution that it's probably under-reporting when our HMOs are doing direct calling people or sending them questionnaires. They get more than that, but I want to emphasize on the serious adverse events because this is what is really important to us, and we had 19 serious reports following the third dose for more than 2.8 million booster dose administered.

Each one of them is being investigated by an independent clinical workgroup using all the data from the hospitals, from the HMOs to try to figure out if this is connected to the third dose or not. So what have we've been getting is seven reports on serious adverse events following the third dose between the ages of 12 to 64. You see how many vaccines it was,

over two million, and we had two allergic reactions that are noted as connected to the third dose. We had a case of myocarditis in a male in his 30s who was hospitalized for two days and discharged

We had a case of Guillain-Barré and Bell's Palsy that is possibly connected to the dose and then three cases of DBT, PE, TIA CVA, and VP in a runner that happened during a routine stress test. All three of them was not deemed connected to the vaccine by the workgroup. Among 65 and above, we see over 800,000 vaccines. We have 12 cases of serious adverse events. The first was suspected encephalitis, the guy who came in with fever and confusion. For him, it was the second time it happened. It happened to him after the first dose. It did not happen after second dose, but it did happen again after the third. And that's a possible connection.

A vitreous hemorrhage that is possibly connected. A CVA that is still under investigation. A bulk of cases, four or five cases, that are infection origin, septic shock, thrombocytopenia due to sepsis.

Three cases of BUTI and pneumonia that was deemed unconnected to the vaccine and then three cases of mortality that was not connected -- people with very multiple comorbidities that had reason for their demise that was not connected to the vaccine. And so the myocarditis focus, I want to emphasize first on this sentence: most young vaccinees received a booster only in the last two weeks, so we don't have a full follow-up for them for 30 days as we want.

We continue to follow them. Another important point is in Israel, because of the myocarditis that was a signal -- we saw in the second dose of the vaccine. We saw increasing cases among young, mainly male, between the ages of 16 to 30. So you see here increasing cases after the second dose, and that was usually after the fourth or fifth day or during the fourth or fifth day after the second dose. So to some extent, we believe that some cases should have popped up in the two weeks follow-up that we have so far for several of the vaccines. But still, we need to be very cautious. We had only one case, as I said, of the 30

something-year-old males.

In the myocarditis cases, we're actually doing active surveillance, so it's not just reporting to us. We are contacting each hospital every week to get all myocarditis cases, not just full-on vaccination, and so we feel here much more safe that it's just not under-reporting effects. The last slide is just really a summary. So the booster dose in Israel was effective and so far has a safety profile similar to the other doses. We saw that the booster dose improves the protection by tenfold against confirmed infection and at least for elderly against severe COVID-19.

What we saw is basically that the post-booster efficacy against Delta was similar to the waning efficacy against Alpha. It's like a fresh vaccine, and the adverse event were not more acute than the first or second. And we didn't see any new severe cases of adverse event. Based on the data that we continuously collect, we are presenting this to our vaccine safety and effectiveness committee, and they have approved by step giving the booster dose after five months to

people starting from 60 and then 50 and then 40. So we are rolling now in the vaccination campaign.

And administration of the booster dose has helped Israel dampen severe cases in the fourth wave. Thank you for your attention.

DR. ARNOLD MONTO: Thank you both so much for this valuable data. I was about to ask a two-fold question, which I usually don't like to allow, but first about myocarditis. But you presented very carefully information, including the fact that younger individuals really have not been heavily vaccinated as yet so the ages there -- the age cut off is hard to determine. One point of information, the second dose in Israel with the Pfizer-BioNTech vaccine was typically given after three weeks or delayed?

DR. SHARON ALROY-PREIS: Yes. Yes, so we started the vaccine campaign after the FDA approval exactly by the protocol approved by the FDA which was three weeks apart.

DR. ARNOLD MONTO: Okay. Thank you. Dr. Pergam.

DR. STEVEN PERGAM: Thank you very much. That was a really thoughtful set of slides, and we appreciate you sharing it with the Committee. I had a question specifically. It seems like you have an opportunity to look at demographic differences between individuals who were eligible to get vaccinated with the booster but didn't -- the group that only received two doses versus those versus (audio skip) received the three. Did you find any demographic differences? You have a really robust medical record.

I'd be really curious to know are there differences that might suggest maybe that the group that received the booster were either higher risk or the differential levels of protection in that.

DR. RON MILO: I can say we definitely looked into this, and there are differences which we account for both in the perform regression and confounders and in the matching approach, also a confounder. We see them, for example, in terms of the tendency to take the third dose, which is different -- the more different, the more graphic groups in Israel society among

different age groups. And this is all reported in the paper that was published. You can see the tables. They're really significant differences, but all of those are supposed to be accounted for inherently in the way we're doing the analysis.

DR. ARNOLD MONTO: Dr. Kurilla.

DR. MICHAEL KURILLA: Thank you, Arnold. I'll see if my camera is actually working this time. Okay. There we go. Yes, it is now. Thank you for the presentation, very insightful. One of the things that stands out for me from your data is that the waning of immunity which seems to be more waning of immunity rather than a Delta-specific phenomena -- although there may be a small component -- it would seem that one would have to conclude that either the mRNA vaccine in general -- that platform or else the shorten dosing intervals is not -- between the two doses -- does not lead to long term good durability of the immune response.

And those individuals at risk particularly for severe disease don't have a good cell-mediated immune

response and are relying on their neutralizing titer other serology which is dropping off rather quickly. Your boost clearly does that, so my question to you is actually two-fold. One, although it's very early, do you have any evidence that the six months boost is actually contributing with a better dosing interval to give you more long term durability in the immune response, and is there any change in the kinetics of the antibody response? Or do you anticipate that just every six months you're going to have to keep boosting these people?

DR. SHARON ALROY-PREIS: So I'll start with the end of your question. I think this is very early. We can't really tell. We know that from some other viruses that sometimes, like in hepatitis, you get a dose and after a month a dose and after six months a booster. And you have protection for many, many years. Whereas for influenza we need to be vaccinated every year, and I think it's not really clear where this is going. We definitely don't have any plans at the moment to boost every six months. We'll base it

exactly as we did here based on the results.

We'll continue to monitor and see if there is, again, any waning effect, but it may be that we won't see that, that after the booster we'll have a higher protection for a longer period of time.

DR. RON MILO: I would add that I think that the effect of the Delta versus Alpha is not very small. I think they're both very significant, both the Alpha versus Delta and the waning. There's also maybe an interaction, a synergistic effect from both of them together. I wouldn't think about it as a small effect.

DR. MICHAEL KURILLA: Thank you.

DR. ARNOLD MONTO: Dr. Levy. Quick questions and quick answers, please. We're going to have time to come back again later.

DR. OFER LEVY: Hello, I'd like to thank the presenters for a wonderful presentation and impressive progress. One question I had was related to the decision to give boosters to the younger individuals as well. As we know, there is some increased risk of myocarditis, particularly in younger males, and it

seemed like there was relatively less data in the younger age groups. So what were the considerations from a policy perspective of recommending a booster for that youngest group? If Dr. Alroy-Preis could say a few words, I'd really appreciate it. Thank you.

DR. SHARON ALROY-PREIS: Sure. So, first of all, we know from research done by (inaudible) HMO in Israel that the risk of myocarditis from corona cells is higher than the risk from the vaccine, and when you have really worrying pandemic with a surge of thousands of cases and doubling every 10 days, the risk of people, even young people, could be infected with corona and get myocarditis is higher than being vaccinated. That risk -- and I have to say that there is a work being published or in the review process from Israel about myocarditis, and in 95 percent of the cases of myocarditis was not severe.

And so we feel that when we weigh a pandemic roaring we saw the productive number of over 1.3 doubling every 10 days the risk even for the young adults would be higher. I have to say something about

a mix of population. So if we only vaccinated the 60 and above, this is roughly 16 percent of our population. Most of our population is younger, and when we looked at the cases -- confirmed cases that we had in the fourth wave, 15 percent of them were 60 and above.

So the majority was not the 60 and above, and we believe that we wouldn't have been able to control the pandemic just by vaccinating those 60 and above. When you have roaring pandemic and we know that the numbers are doubling, then we really have to make sure that we get to a reproductive number under one in order to control it. We wouldn't have been able to do this, we think, just by vaccinating the 60 and above.

DR. OFER LEVY: Secondly, any sense of the --

DR. ARNOLD MONTO: We're going to have to move on. We've got a list of about eight people who want to ask questions. Dr. Gans. Go ahead, please. Dr. Gans? We're going to have to move onto Dr. Rubin until Dr. Gans --

DR. HAYLEY GANS: Sorry. Sorry.

DR. ARNOLD MONTO: Okay, Dr. Gans, quickly.

DR. HAYLEY GANS: Thank you. This is wonderful and very provocative given that you were ahead of us, so it's foreseeing the future. So thank you for sharing your data. I had a question because not only in as you suggested in your last answer in order to really control a pandemic we have to control secondary cases, so the ability to spread -- and what we are starting to see is in our vaccinated households we are starting to see spread into our younger populations who are no longer seemingly protected by herd immunity around them.

Were you able to look at the secondary cases within households? You have the opportunity to do that. People are being tested. So what is the lack of protection for children when you started seeing those surges, and then was there any control of that protection to those in our societies who haven't been able to be vaccinated?

DR. ARNOLD MONTO: A quick answer to a complicated question, please.

DR. SHARON ALROY-PREIS: We'll do our best. So our fourth wave actually started with younger people coming from abroad and their kids -- the older adults were vaccinated. The kids obviously were not. We saw a surge in cases among both, and that was the beginning of our fourth wave in kind of two spots and then spread in a community wave. What we saw in the beginning of June is that the ability of the vaccinated individual to spread it to others was lower than in the non-vaccinated. So roughly 80 percent of the people who were vaccinated at the beginning -- who were vaccinated, did not infect others outside their household.

In their household, it was highly contagious, so vaccinees that became confirmed cases were infecting their household. And that actually led us to a policy that said if you have a confirmed case at your household and you need to take care of him, a child, you can't really go in and out taking care of him because you will be infected, and you will infect others going to work. So we definitely see that cases

that are doubly vaccinated that are no longer fresh, what we call -- more than six months from the second dose are infecting other people.

It's obviously less than non-vaccinated, but we're seeing that, especially in their household.

DR. ARNOLD MONTO: Dr. Rubin, the final question before we are forced to take a break.

DR. ERIC RUBIN: Thanks, Arnold. Thank you very much for the presentation and for generously sharing the data. The Israeli data are very important for all of us making these decisions, so it's been a great laboratory. And you've done a very nice job of it. Dr. Gans just mentioned how one of the goals would be to prevent transmission and reduce the size of the epidemic. But, of course, another goal is preventing severe disease. If you look at it through that lens can you identify the people who are likely to get severe disease?

Do they look like the people at high risk otherwise? In other words, could you focus the administration of a third dose of vaccine on particular

groups to give a very high yield for preventing severe disease?

DR. SHARON ALROY-PREIS: The obvious question is those who are 60 and above and those who have comorbid conditions, especially morbid obesity. We see that as very clear chronic disease that is a risk factor for COVID-19. However, as I said before, having about 16 percent of the population over 60, it's really very -- we can't imagine just vaccinating that group knowing that 85 percent of the confirmed infections are among the rest of the population and trying to get to a reductive number of under one so this pandemic starts to shrink, this wave will start to fall.

We have to -- in our opinion in Israel, we had to vaccinate more than just 16 percent of the population to get there. So we definitely see mortality among young people who are not vaccinated -- 30, 25, 41, really young people, and we started to see the same trend of severe critically ill patients among those who were 40 to 60 and have been doubly vaccinated. And we just didn't want to wait to see

those results, and we knew that we needed to vaccinate larger proportion of the population in order to get the numbers down quickly.

I have to add one more thing. We always look at the severe and critical disease status or mortality. I think there is also importance in long COVID among those who are infected and so we can't really put this aside and say this is influenza. If you went through this it's fine. We see that there is high percentage of people, including young people, who are left with symptoms for over a month. So there's several reasons why we wanted to make sure that we overcome this fourth wave.

DR. ARNOLD MONTO: Okay. Thank you so much. A very good and very informative presentations and a very vigorous discussion which actually will be continued in the question and answer session which comes later. I hope our speakers from Israel especially where there's a seven-hour time difference will be able to stay with us, and from the UK as well, for that discussion later on. So five minutes for a

break and then we resume again.

DR. SHARON ALROY-PREIS: Thank you.

[BREAK]

SPONSOR PRESENTATION

MR. MICHAEL KAWCZYNSKI: Welcome back to the 167th VRBPAC meeting. We will get started with -- that was a nice little, short break. I will hand it back to Dr. Monto. Take it away.

DR. ARNOLD MONTO: Thank you, Mike. We're about to move to the sponsor presentations. We're going to be hearing about the effect of the booster shot, and we're going to be listening to presentations from Donna Boyce, senior vice president Global Regulatory Affairs at Pfizer, and from Dr. Bill Gruber, senior vice president at Pfizer. Take it away.

MS. DONNA BOYCE: Good morning, members of the committee, FDA, and ladies and gentlemen in the audience. It's a pleasure to be here today. I'm Donna

Boyce, and I'm the senior vice president of global regulatory affairs for Pfizer. I would like to thank the FDA for organizing this VRBPAC and the VRBPAC chair and members for their time. Pfizer and our partner BioNTech are pleased to be here to today to discuss a revision to the dosing schedule for our mRNA COVID-19 vaccine. Our presentation today will follow this agenda.

After I provide a brief introduction, Dr. William Gruber, senior vice president in vaccine clinical R&D, will review the Booster Clinical Development Program, including the neutralization data from phase one, the phase three immunogenicity and safety results, the pharmacovigilance plans, real world evidence supporting the use of a booster, and a benefit-risk conclusion. After this, I will come back to provide conclusions for our presentation.

The Pfizer-BioNTech COVID-19 vaccine, also known as BNT162b2, has been available for the prevention of COVID-19 disease in individuals greater than or equal to 16 years of age since December 2020

under the Emergency Use Authorization and in individuals greater than 12 years of age since May 2021. To date 1.7 billion doses have been distributed globally. Between February and May 2021 and in accordance with FDA guidance, we conducted a pivotal clinical study to evaluate the safety and effectiveness of a booster dose.

FDA granted full BLA approval of BNT162b2, also known as Comirnaty, on August 23rd for the prevention of COVID-19 disease in individuals greater than 16 years of age as a two-dose series given three weeks apart. The duration of protection following the two-dose primary series is currently unknown, but available data suggests that efficacy wanes over time. Based on the positive results of the booster dose study, available real-world evidence, and in consultation with the FDA, on August 27th we submitted an supplemental Biologics License Application to seek approval of a single booster dose after the primary series.

There is substantial randomized controlled-

trial data and real-world evidence to support that vaccine efficacy waned over time. As you heard earlier, recent data from Israel and the United States in the context of the Delta variant of concern suggests that vaccine protection against COVID-19 infection wanes approximately six to eight months following the second dose. A retrospective real-world evidence cohort study conducted at Kaiser Permanente Southern California suggests that the observed erosion in vaccine effectiveness is likely primarily due to waning effectiveness rather than do to Delta escaping vaccine protection.

Waning effectiveness over time is further supported by a recent FDA-requested post-hoc analysis of breakthrough cases in the pivotal Phase three efficacy study. To demonstrate the safety and effectiveness of a booster dose against COVID-19, Pfizer and BioNTech conducted a sub study of the phase three pivotal study that complies with the FDA guidance. The results of this study demonstrate that a booster does of BNT162b2 has an acceptable safety

profile and elicits robust immune responses.

Finally, real-world evidence from a recently initiated booster vaccination program in Israel that we just heard in the face of waning immunity and in the period when the Delta is the dominant, shows the booster dose has a reactogenicity profile similar to that seen after receipt of the second primary series dose and restored high levels of protection against COVID-19 outcomes. The booster study was conducted in individuals 18 to 55 years of age, as recommended in the FDA guidance.

The study was conducted in two phases. Phase one demonstrated that a booster dose administered approximately six months after the second vaccination of our vaccine had an acceptable safety profile and elicited robust immune response against the wild type as well as the Beta and Delta variants of concern. Phase three showed that the vaccine was as well tolerated as the second primary dose and elicited immune responses against the wild type variant that were noninferior to the immune response observed after

the second primary dose, meeting the protocol-specified immunobridging success criteria for GMTs and seroresponse rates.

Moreover and in accordance with FDA guidance, the safety and effectiveness of the booster dose in individuals 18 to 55 years of age can be extrapolated to individuals 16 and 17 years of age and over 55 years of age. These data serve as the basis for the Supplemental Biologics License application. During the remainder of our presentation, we will share data with you demonstrates that the overall benefit-risk of the booster dose is favorable, specifically that the demonstrated safety and effectiveness of a third dose supports adding a booster dose to the vaccination schedule and the global real-world evidence demonstrates that the reduction in vaccine efficacy is likely due to waning effectiveness and supports that a booster dose can restore high levels of protection with an acceptable safety profile.

Based on these, we're requesting licensure of a single booster dose of BNT162b2 administered

intramuscularly at least six months after the primary series in individuals greater than 16 years of age. I will now turn our presentation over to Dr. William Gruber, who will present clear and compelling data demonstrating the booster safety, immunogenicity, and effectiveness. Bill?

DR. WILLIAM GRUBER: Thank you, Donna. It's my pleasure to share with you today the clinical program that supports the safety and effectiveness of a booster dose. I have three goals in my presentation this morning. First, I will speak to the public health need that could be well served by a booster. Second, I will describe the clinical trial and real-world effectiveness data supporting the safety and effectiveness of the booster dose. Third, I will conclude with overall benefit-risk of a booster dose.

Let's begin. There is clear erosion of vaccine protection over time against COVID-19, and emerging data indicates loss of protection against hospitalization. We need to maintain high vaccine effectiveness against COVID-19 to contain the pandemic.

A safe and effective Pfizer-BNT vaccine booster dose for individuals 16 years of age and older would be expected to restore protection and reduce COVID-19 illness and spread. The BNT162b2 vaccine is highly protective against COVID-19, but the duration of protection wanes over time.

Let's talk about the lines of evidence supporting this claim. First, data from the pivotal phase three clinical trial showed that two doses of the Pfizer-BioNTech vaccine administered three weeks apart confers protection against both symptomatic and severe COVID-19. That of course was the basis for the emergency use authorization and the recent licensure of the COVID-19 vaccine in individuals 16 years of age and older. The full duration of protection of the Pfizer-BioNTech vaccine is currently unknown.

An analysis of efficacy up to 6 months after dose 2 from the pivotal clinical trial shows that initial vaccine efficacy slightly wanes over time in the pre-Delta period from 96.2 percent in the first 2 months after vaccination to 90.1 percent over 4 months

and is still sustained at 83.7 percent up to approximately 6 months. Further waning of immunity and protection over time has been observed across the world coinciding with penetration of the Delta variant.

Originally observed in Israel, as you heard, this is now being observed in the United States and elsewhere. As we all know, the Delta variant became widespread globally as of June and July of this year. Reports describing reduced effectiveness of the Pfizer vaccine and other COVID-19 vaccines against SARS-CoV-2 infections caused by Delta have surfaced from Israel, the United States, and Qatar, as you've also heard early this morning.

Recently in Israel, reduction in vaccine effectiveness has been observed against hospitalization and severe infection over time after a two-dose Pfizer vaccine primary series. Again, you heard details about this earlier today from the Israeli Ministry of Health. In addition, recent US CDC data hint at reduced COVID-19 vaccine effectiveness over time against severe disease and hospitalization in the US.

This reduced vaccine effectiveness tracks with longer spans of time between two doses of vaccine and SARS-CoV-2 exposure. Vaccine effectiveness studies to date have not adequately differentiated the impact of Delta from potential waning immunity on recent reductions of vaccine effectiveness. In collaboration with Kaiser Permanente Southern California, Pfizer evaluated overall and variant-specific real-world effectiveness of the Pfizer vaccine against SARS-CoV-2 infection and COVID-19-related hospitalizations by time since vaccination. This was done to further inform issues of waning immunity and protection.

Let's first take a look at the methods that were used in the Kaiser trial that informed thinking. The setting is the Kaiser Permanente Southern California group, which includes over 3.4 million members greater than 12 years of age who would be potential vaccine recipients. The study period includes December of 2020 through August 8th, 2021. This encompasses both the period when, first, the Alpha and later, the Delta variants were present. Whole

genome sequencing has been done on all samples obtained during this period as part of this trial.

A cohort approach was used using Cox models. Again, this looks for both outcomes of infection as well as COVID-19-related hospitalization as defined in the footnotes shown at the bottom of the slide. The vaccine status was evaluated with those fully vaccinated with two doses of vaccine at least seven days after the second dose. This also looked at attack rates in the unvaccinated as a comparator. Here's the first key observation: vaccine effectiveness waned over time against infections but, as of this summer, had not yet waned against hospitalization in the Kaiser Permanente study.

Let me describe for you the data that supports these observations. If we start on the left-hand side, you see the graph titled "SARS-CoV-2 Infection". On the X axis are represented months after full vaccination, and on the Y axis, adjusted vaccine effectiveness. Each of the colored lines represents a different age group from 12 to 15 years of age up to

adults 65 years of age and older. The black line represents all individuals 12 years of age and older. Vaccine effectiveness against circulating virus at each time point is shown as a corresponding number above the X axis.

Vaccine effectiveness was 88 percent in individuals one month after 2 doses of the Pfizer vaccine in this study. As you can see, for all age groups 16 years of age and above, efficacy wanes over time, dropping to 47 percent for those individuals out more than 5 months from completion of the two-dose series. For 12 to 15-year-olds, efficacy may be somewhat better sustained, perhaps consistent with higher virus neutralization levels achieved in this age bracket.

However, follow up is of shorter duration due the more recent approval of vaccine for this age group. If we look on the right-hand side, we see, in contrast to effectiveness against infection, effectiveness against COVID-19-related hospitalization has been sustained over this period of time in all age groups

from 12 to 15 years of age to those over 65 years of age out to at least 5 months. You can see that the efficacy for those vaccinated at less than 1 month is 87 percent. For those vaccinated at greater than 5 months, it's still around 88 percent.

Now, please keep in mind what you heard earlier from the Israeli Ministry of Health. Effectiveness against severe disease and hospitalization has begun to decline in Israel. The combination of early, comprehensive immunization and a high proportion of the population more than six months postvaccination in Israel may have contributed to this early signal in Israel. These results, along with recent CDC data, pretend that effectiveness against COVID-19 hospitalization and severe disease are less likely to remain sustained in the future in the US.

We may see similar increases in hospitalizations and severe disease in weeks to months for those individuals vaccinated early in the US campaign. If so, the time to restore protection with a safe and effective booster dose of BNT162b2 is now.

It's important also to look at the relationship between vaccine effectiveness and the variants that are circulating. A second key observation from the Kaiser study becomes clear: vaccine effectiveness wanes over time irrespective of the variant of concern.

What is the evidence to support this claim? Again, the orientation of this slide is much the same as you saw previously. Months after full vaccination are shown on the X axis, and adjusted vaccine efficacy is shown on the Y axis. Whether we examine other sequenced SARS-CoV-2 variants, represented by the black line, or the Delta variant, shown in the blue line, the vaccine effectiveness over time wanes. Point estimates of vaccine effectiveness are lower for the Delta variant after completion of a two-dose vaccine series but a number of the confidence intervals overlap.

Most prominently, comparative data shown here supports that declining immune response over time is the primary driver of vaccine effectiveness and not variant escape. Restoration or improved immune

response by a booster BNT162b2 dose would be expected to restore the comparable high protection against Delta and other variants seen at the left end of the graphs. We also have additional information gleaned from the pivotal clinical trial that informs this thinking.

This type of randomized control analysis was noted to a best practice by Dr. Sterne earlier today. It reveals waning protection between 5 and 10 months after 2 doses of the Pfizer vaccine. As shown in the top graphic, this evaluation was done in the pivotal phase three efficacy trial in individuals over 16 years of age who completed the two-dose series early in the study, the original vaccinees, to participants who were in the placebo group that crossed that crossed over to the vaccine after the vaccine received emergency use authorization.

This permitted evaluation of the difference in incidence rate and relative protection against COVID-19 for those who received vaccine proximate to the Delta surge, the crossover group, versus those who received vaccine more remotely, the original vaccinees. The

text at the bottom, beginning on the left, describes the results: the meantime from dose 2 to July the 1st is 4.7 months for the crossover group and 9.8 months for the original vaccine group, providing a separation in time that allows one to differentiate a potential effectiveness perimeter on immune response and protection.

Ninety percent of the crossover group received dose two less than six months prior to July the 1st. Almost all in the original vaccinee group received dose two more than eight months prior to July the 1st. Relative vaccine efficacy comparing those immunized later compared to those immunized earlier was 26.3 percent. If we assume for a moment that protection against COVID-19 falls below 70 percent, which is reasonable based on trial data as well as the Kaiser data I've shared with you, and that it falls below 70 percent at 5 months after vaccination, efficacy by extrapolation would be expected to be below 60 percent at 10 months compared to those that were unvaccinated.

Difference in incidence rates calculate as

18.6 cases per 1,000 person-years of follow-up. The magnitude of this risk highlights the public health importance of time when one extrapolates this to the millions of individuals who may remain at risk in the setting of Delta variant or other variant spread. Over a year's time, 1.86 million more cases might be expected to occur in 100 million individuals similarly exposed over a year who are 10 months out from a two-dose series compared to those 5 months out from a two-dose series.

A safe and effective booster dose of the Pfizer-BioNTech vaccine would be expected to narrow this gap. Let me summarize then the public health need that leads us to conclude that a safe and effective booster would be beneficial. Israel and United States real-world evidence suggests that vaccine efficacy against COVID-19 infection wanes approximately six to eight months following the second dose when the Delta variant is predominant.

A retrospective Kaiser study suggests that vaccine efficacy reductions are primarily due to waning

vaccine-induced immunity rather than due to Delta escaping vaccine protection. Waning vaccine effectiveness is further supported by the recent FDA requested post-hoc analysis of breakthrough cases in the pivotal phase three clinical study. While waning vaccine efficacy against hospitalization was not observed in the United States, this should be carefully monitored as data from Israel suggests that reduced effectiveness against severe disease could eventually follow reductions in vaccine effectiveness against SARS-CoV-2 infections.

The Israeli experience could portend the US COVID-19 future and soon. The information I've presented to you speaks to the importance of waning protection and a compelling rationale to restore protection. What information do we have that reassures us about the safety and potential effectiveness of a booster dose to meet that need? I'm going to share that with you now.

First, it is important to understand the nature of responses across not only the current

variants of concern but variants that may be of concern in the future as we contemplate the advantages of a booster dose. For this, information that we have after two doses of the Pfizer-BioNTech vaccine are reassuring. The vaccine-elicited Sera effectively naturalize a broad range of SARS-CoV-2 spike variants after two doses of the Pfizer-BioNTech MRNA vaccine.

You can see this is true whether we're talking about the wild type variant, the previously prominent Alpha variant, the Beta variant, or the more recent Delta variant. I would highlight that even in the circumstance associated with the lowest response seen here, a GMT of 194 to the Beta variety, efficacy was observed in the south African cohort from our pivotal trial. You will recall that we demonstrated a case split of 0/9, vaccine versus placebo, 8 of whom had a specimen successfully sequenced to reveal that the virus was the Beta variant.

This provides the following reassurances: so far, immunologic escape from Sera neutralization after two vaccine doses has not been demonstrated. Given

that a second Pfizer-BioNTech vaccine dose is associated with robust antibody responses across variants of concern, increased responses to vaccine virus, what we reference as wild type virus, after a third dose should also be associated with increased neutralization response to variants of concern.

I will share with you evidence that supports this logic. First, I want to remind you about the original pivotal study design which was used for us to examine a booster dose. This slide may look familiar to you because it's similar to what was presented at the time of emergency use authorization. The vaccination period for the purposes of this trial for the two primary doses were 21 days apart.

As you can see represented on the graph, individuals had active surveillance performed to look for COVID-19 illness in association with nucleic acid amplification as positive evidence of SARS-CoV-2 infection. As you can see, the length of times that were used to follow-up for reactogenicity shown in the green: one month for non-serious AE, six months for

serious AEs and up to two years for deaths accruing in this population including older adults and those with comorbid conditions.

Now, I want to share with you where we are today. This graphic represents the experimental design of a third dose of vaccine administered to individuals recruited from the phase one and phase three phase of the pivotal safety and efficacy trial. Again, we took the population who had received their original 2 doses 21 days apart.

For phase one, we went to the sentinel cohorts who were first immunized as part of our trial in May of last year, which represented 23 individuals, and administered a booster dose obtaining the safety information as well as serum samples to measure immune response over the time periods shown. Lighter blue represents days, darker blue months. After we gained sufficient information from phase one that reassured us about the safety and immune response to the vaccine, we then moved to the expanded group that recruited from the phase 2/3 portion of the pivotal trial.

These individuals were now approximately seven months post dose too. There were 312 of them in the group who were boosted. Again we tracked reactions, adverse events and obtained blood specimens as shown to monitor safety and immune response. Let me summarize for you first the data from the Phase one part of this trial. I'm going to begin with immunologic responses. Post-dose three BNT162b2 indicate a substantial boost and reduced gap between the wild type and Beta neutralization with the boost. The Beta variant was chosen at the time because of concern about potential for spread and is a surrogate for other variants.

Let me now share with you the evidence that supports this statement. First, let's examine the 18 to 55-year-old group on the left-hand side of the slide. The X axis represents the time of dosing and measurement of antibody response and the Y axis represents 50 percent serum neutralizing titer to SARS-CoV-2. If we begin with those individuals who received two doses of vaccine, the primary series, you can see that for both the wild type and Beta variant tested in

this trial that there were robust antibody responses that were most prominent seven days after dose two.

These began to decline as soon as one month after dose two and were still lower before dose three. If you then look at the response after administering the booster, there are at least three important observations. Number one, there's a dramatic increase in the antibody response as measured by GMTs for both the wild type virus as well as the Beta variant at seven days after dose three as well as one month after dose three.

Number two, the difference between the response of the wild type and Beta variant has narrowed, represented by the geometric mean ratio shown at the top. The ratio one month after dose two is 0.27. One month after dose three, this ratio is 0.73. We see a narrowing of the geometric mean ratio and therefore narrowing of difference between immune response to the wild type vaccine virus and the Beta variant after the third dose.

Number three, in contrast to the decrease in

antibody response seen seven days after dose two to one month after dose two, we actually see an increase in antibody response between seven days after dose two and one month after dose three. What does all this mean? Our interpretation is that we're seeing a robust immune response that equals or greatly exceeds the response that we've seen after the second dose.

This response continues to mature as evidence by a continuing increase in antibody response at one month and narrowing of the difference in geometric mean ratio between the response to the wild type and Beta variant. This bodes well for comparable and perhaps improved protection after a third Pfizer-BioNTech vaccine dose. Again, on the right-hand side of the graphs, these observations are recapitulated and perhaps even more important in the 65 to 85-year-olds.

Why? Responses after the second dose of vaccine tended to be lower and decayed more rapidly than in younger adults. But look what happens after the third dose: higher antibody response are seen seven days and one month after dose three compared to those

after the second dose and closely rival those seen in younger adults. There is again narrowing of the GMR between wild type and Beta variant and an increase in response over time.

This suggests a significant immunologic benefit of a booster dose of the vaccine that is likely to confer similar or perhaps better protection than that provided by the second dose. This information was published in the *The New England Journal of Medicine* this week. Now, of course it's important to know does this apply to the Delta variety since that's the variant of current concern? I'm pleased to report the post-dose three Pfizer-BioNTech GMTs indicate a substantial boost to the Delta variant similar to that seen with wild type.

This information is also included in *The New England Journal of Medicine* publication. Here we've represented for you the responses one month after dose two compared to one month after dose three with a similar scheme as shown on the prior slide: younger adults on the left, and older adults on the right. We

again see a dramatic increase in immune response after the third dose as measured by virus neutralizing GMTs to both wild type virus and the Delta variant and a narrowing of the GMR point estimates as shown at the top after the third dose.

Note that this narrowing of response is most prominent in the older age group. This provides further reassurance that a third dose of vaccine is likely to provide immunologic benefit, restoring and perhaps improving protection against the Delta variant. Given the observations I shared you earlier about lack of immunologic escape for variants tested to date after two doses, these observations inspire optimism about the potential for a high level of protection against current and future variants after a third vaccine dose.

What about reactions seen in phase one? In the phase one cohorts of younger and older adults, the evidence was reassuring that local reactions by maximum severity within seven days of the third dose, the bottom panel, were similar to those after dose two, the top panel. The local reactogenicity captured by eDiary

revealed no redness or swelling and comparable pain. Also, systemic events by maximum severity within seven days after the third dose were similar after dose three compared to dose two.

We have found fever and chills to be the most discriminating common reactions. In the phase one cohorts comparable levels of fever and a comparable level of chills were seen after dose three compared to dose two. Other reactions were also comparable. This safety information coupled with the proceeding immune response data gave us confidence that we could move forward into the expanded cohort. Let me now summarize for you the phase three portion of this booster study.

To begin, I will describe for you how this phase three study was designed by Pfizer and approved by the FDA to support a booster dose indication in the individuals 16 years of age and older. This FDA-approved approach is based on meeting predefined safety and immune response criteria in the 18 to 55-year-old age group with extrapolation to the full age range 16 years of age and above.

What is the basis for extrapolation of phase three third dose data to 16 to 17 and greater than 55-year-olds? The FDA immunogenicity requirement is outlined in the text shown and referenced by the footnote. It reads, "Studies may be conducted in a single age group, for example adults 18 to 55 years of age, with extrapolation of results to other age groups for which the prototype vaccine has been authorized."

Meeting this requirement was judged by CBER as sufficient to submit immunologic data for a supplemental licensure of the Pfizer-BioNTech vaccine third dose. Regarding extrapolation of safety to the full age range, a few observations are pertinent. For 16 to 17-year-olds similar reactions in this age group to 18 to 55-year-olds after doses predicts that reactions would also be similar after the third dose. For adults over 55 years of age, local reactions and systemic events in participants greater than 55 years after dose two were lower than those seen in younger adults.

This predicts lower reactions after the third

dose in individuals greater than 55 years of age based on the favorable or better reactogenicity profile seen after the third dose compared to the second dose in 18 to 55-year-olds, data that I'll be sharing with you shortly. Now, to interpret these results in the context of what we're seeking today, it's important to understand the FDA immunogenicity criteria for a booster dose.

The FDA guidance specifies that the booster dose must be adequately powered to demonstrate that the immune responses induced by the boost, serum neutralizing titers against SARS-CoV-2 as measured by seroresponse rates and GMTs, are statistically non-inferior compared to those elicited by the vaccine in the primary series.

How do we do that? The success criteria include demonstration of noninferiority margins of -10 percent for seroresponse rates and one and-a-half fold for GMTs. Based on consultations with CBER, these criteria are also considered sufficient to support licensure of a booster following full approval of the

primary series. This table shows the demographics of subjects receiving the third dose. These demographics are representative of 18 to 55-year-olds in the parent study.

Note that we have a balanced representation across gender, races and ethnicity. Over 50 percent of individuals had comorbidities as measured by the Charlson comorbidity index. The age of vaccination was approximately 41. The time from dose two to the booster was close to seven months with a minimum of approximately five months --

MR. MICHAEL KAWCZYNSKI: Let's see. Pfizer, you're back connected.

DR. WILLIAM GRUBER: Thank you. Let me maybe start a little bit back to make sure that everybody gets to hear what I had to say. This table shows the demographics of subjects receiving the third dose. These demographics are representative of 18 to 55-year-olds in the parent study. Note that we have a balanced representation across gender, races, and ethnicity. Over 50 percent of individuals had comorbidities as

measured by the Charlson comorbidity index. The age of vaccination was approximately 41.

The time from dose to the booster was close to seven months with a minimum of approximately five months and a maximum of eight months since the two-dose series. Let's look at the immune response data. Recall that the study needed to be two immunologic criteria for noninferiority based on comparison to geometric mean virus neutralization titers and seroresponse after the third dose to those responses seen after the second dose.

The geometric mean ratio of neutralizing titers noninferiority criterion, post dose three compared to post dose two, was met with titers after the third dose approximately three-fold higher than those seen after the second dose. This table shows SARS-CoV-2 neutralization titers in 210 individuals looking at 1 month post dose 3 compared to the GMTs after dose 2. The GMR is the ratio of these responses.

To declare success the lower bound of the confidence interval for the GMT on the right-side of

the table needed to be above 0.67 or two-thirds. We see that the lower bound greatly exceeds this success criteria at 2.76 with a GMR point estimate indicating responses were three fold higher after the booster dose compared to responses after dose two.

Hence, this meets not only the noninferiority criteria but indicates that the virus neutralization responses seen after the third dose are consistent with phase one results and greatly exceed and are statistically greater than those seen after the second dose. This figure demonstrates graphically the SARS-CoV-2 neutralization GMTs with relationship to those. GMTs shown are based on the number of subjects without results at each time point, while the noninferiority analysis for the GMT ratio shown on the prior slide are based on subjects who had valid results at both one month post-dose two and one month post booster.

Time and doses are shown on the X axis, 50 percent neutralizing GMTs on the Y axis. Results are consistent with those seen in the phase one study. Neutralizing GMTs rise to protective levels after the

second dose, followed by a drop prior to the third dose. By seven days after dose three, observed virus neutralization GMTs are nearly double and by one month are triple those achieved after the second dose.

These results indicate that a third dose is likely to begin conferring benefit shortly after administration. Noninferiority of the booster dose was also demonstrated based on proportion of subjects with a seroresponse meeting the second immune response licensure criterion. Seroresponse is defined as achieving a greater than or equal to four-fold rise from baseline before dose one. In this population of 198 individuals, the 1 month post-booster response was 99.5 percent after dose 3 versus 98 percent after dose 2 when both were compared to baseline.

This yielded a one-and-a-half fold greater response after the booster with the lower bound of the confidence interval of -0.7 percent, well above the -10 percent required. Noninferiority was also confirmed based on an FDA-defined alternative analysis. We were asked by the FDA in a post-hoc analysis to compare pre-

booster versus post-booster seroresponse.

You can see that with this analysis in 179 individuals, the seroresponse rate was 93.9 percent post-dose 3 versus 97.8 percent post-dose 2, again meeting the -10 percent noninferiority criteria with the percentage of the lower confidence interval being -8.2 percent. Both the prespecified GMT and seroresponse results as well as the post-hoc alternative seroresponse rates satisfied licensure criteria for a booster dose with neutralization GMTs greatly exceeding those seen after dose two.

Now, I want to share with you the safety data that supports a booster dose. Follow-up time for the booster dose study is shown here. Total exposure from booster vaccination to the data cutoff date was a mean of --

DR. ARNOLD MONTO: Bill, could you please wrap up pretty soon? You're running out of time.

DR. WILLIAM GRUBER: All right. Let me get through the safety information. I thought we had 45 minutes. Are we running close to that?

DR. ARNOLD MONTO: You are.

DR. WILLIAM GRUBER: Okay. We'll move quickly through this. Follow-up time for the booster dose study is shown here. Total exposure from booster vaccination to the data cutoff date was a mean of 2.7 months and a median of 2.6 months with the ranges shown. The total exposure from dose 2 to the cutoff date, including both exposure post-dose 2 as well as that post-dose 3, was a mean of 9.4 months and a median of 9.5 months.

Let's look at the reactions solicited by eDiary after the booster dose compared to reactions after dose two. Local reactions after dose three were comparable to those seen after dose two. Reactions after dose three are in the bottom panel, dose two in the top panel. I think you can see these recapitulated results that we saw in phase one. This provides reassurance of comparable local reactions with a booster dose. Likewise, systemic events by maximum severity within seven days of the third dose are similar to post-dose two.

Again the same scheme, dose three in the bottom, dose two in the top panel. I again draw your attention, particularly, to fever and chills who are in this larger data set. You can see that, if anything, the fever point estimate is lower than that seen for fever after the second dose in this cohort of 18 to 55-year-olds. Reported chills are also lower and other reactions are comparable to those seen after the second dose. This provides reassurance that the eDiary reactogenicity profile after a third dose is similar or perhaps even better than that seen after the second dose.

Adverse events by system organ class occurring in greater than one percent of participants with one month post-dose third dose were less than those post-dose two in the parent study with the exception of lymphadenopathy. Adverse events after dose three are shown in dark blue bars, adverse events after dose two, little blue bars. At the top of the graphic chart, blood and lymphatic disorders at 5.2 percent is entirely represented by axillary lymphadenopathy. By

comparison after dose 2, 0.5 percent of the 0.6 percent in this category is also represented by lymphadenopathy.

Generally, lymphadenopathy after dose three was mild, self-limited and resolved. Lymphadenopathy includes one individual who's lymph node enlargement was judged severe by the investigator due to reported prevention of arm movement. It lasted for five days and resolved. For reactions other than blood and lymphatic disorders as shown on this graphic, the incidence of adverse events was typically lower or comparable after dose three. These AE findings are reassuring regarding the safety profile of the vaccine. There were no SAEs or withdrawals due to SAES in the one month period after the third dose.

Only one serious adverse event was observed through the median of 2.6 months of follow up at the time of data cutoff, which was assessed as unrelated to the vaccine. This was a myocardial infarction reported 62 days after dose 3 by an individual in their 40s. The event was considered unrelated to study

intervention by the investigator. This individual had a medical history pertinent to the etiology of a myocardial infarction and the cardiac event was considered secondary to stimulant abuse.

The myocardial infarction was reported as recovered and resolved without sequelae within one day of onset following treatment. Details of this case are included in the briefing document. You may recall a version of this slide from the emergency use authorization which has been annotated somewhat to reflect the ongoing work that is done. You can see the nature of the pharmacovigilance that we are conducting. Pharmacovigilance activities are a critical component of activities relating to the detection, assessment, understanding and prevention of risk.

Pfizer has been conducting robust pharmacovigilance activities and collaborating with regulators and international groups. We will continue to look for rare adverse events such as myocarditis, anaphylaxis, as well as other adverse events of special interest. The current approach to pharmacovigilance

has been valuable in detecting and assessing rare events and risks. We will continue these --

DR. ARNOLD MONTO: You're really at the end of your time, Bill.

DR. WILLIAM GRUBER: All right. The evidence to date supports a positive risk benefit for the Pfizer-BNT vaccine. Let's go to the next slide, please.

DR. ARNOLD MONTO: You're really over your time, and the FDA has to be able to speak.

DR. WILLIAM GRUBER: I understand. Let me just recapitulate. You've already had a chance. Can we go to the next slide, please? Information has been shared with you earlier -- you heard earlier from this morning. A third booster dose restored high level of effectiveness for preventing both infections and severe COVID-19. This table represents --

DR. ARNOLD MONTO: We've already heard the Israeli data.

DR. WILLIAM GRUBER: All right. I think the point is that we obviously have seen a dramatic fold

reduction by 11 fold for infection and 15-and-a-half fold for severe infection that we believe a booster dose can restore. With that, I will turn this over to Donna Boyce to wrap up.

DR. ARNOLD MONTO: I think we've already had a wrap up. Thank you both very much. We will have a Q&A session later on in which you all will be able to participate. Let's go on now and hear the FDA presentation from Dr. Joohee Lee. Dr. Lee, please.

FDA PRESENTATION

DR. JOOHEE LEE: Good morning everyone. I am Dr. Joohee Lee. I'm a medical officer at the Office of Vaccines Research and Review within the Center for Biologics Evaluation and Research at the FDA. Here is an overview of the presentation today. I'd like to mention that these slides are a collective effort of many members of the Office of Vaccines.

To quickly go through this, on August 23rd, 2021, FDA approved the BNT162b2 vaccine under the

proprietary name of Comirnaty for active immunization to prevent Coronavirus disease 2019 caused by SARS-CoV-2 in individuals 16 years of age and older. It's currently the only vaccine or medical product that is FDA approved for the prevention of COVID-19. The BLA supplement being discussed to today is intended to support approval for booster administration of Comirnaty approximately six months following the primary series.

I will start with the regulatory background with some key dates. In April 2020, starting on the left, the pivotal parent study C4591001 enrolled the first patient. In December 2020 an EUA was issues for the primary series in individuals 16 years of age and above. In May 2021 it was extended to individuals 12 years of age and above. On August 13th, an EUA was issued for a third primary series dose for immunocompromised individuals. In August, as I previously mentioned, on the 23rd we licensed the primary series of Comirnaty in individuals 16 years of age and above.

Let me go through the boost study design. As previously mentioned, this starts with a parent study, during which over 44,000 individuals were randomized to receive Comirnaty or saline placebo, two doses given three weeks apart. Now, after serial unblinding, a number of individuals received a booster dose, first in phase 1 where 23 adults received their booster dose approximately 8.2 to 8.4 months after dose two, and in 306 individuals from the phase 2/3 portion who received it in a median of 6.8 months after dose 2.

Safety data were collected uniformly as shown in the boxes below with solicited, unsolicited, serious adverse events, and death and serious adverse events that were deemed related to be collected for up to two years after dose two. I'll point out that the data to be discussed today will be from the subset of the 44,000 for the first 2 doses. Let's skip over to give you an overview of the demographic profile for the booster dose participants.

The phase one participants were very homogenous. As you can see on the bottom bar or

section below, none were obese. None had comorbidities or history of SARS-CoV-2 exposure pre-dose one. The homogeneity is mostly a function of the eligibility criteria for the study at phase one and development. In the last column you see, as you've seen before, the profile for participants in phase two and three. We see some greater diversity in race, predominantly white at 81 percent and some with history of SARS-CoV-2 exposure at 3.6 percent.

Any of the comorbidities being to confer increase with severe COVID excluding obesity was at 18.3 percent and approximately 40 percent with obesity. We'll move onto the immunogenicity results. The primary immunogenicity objective was to demonstrate noninferiority of neutralizing antibody geometric mean titers against the reference or the wild type SARS-CoV-2 strain, USA_WA1, which is Wuhan-like. It was measured after the booster dose and compared to after the two-dose primary series in the same individual. You can see in the pictorial above the four timeframes of interest. That will be discussed in the subsequent

slides.

Another point to make is that the immunogenicity data can use in a validated virus microneutralization assay to quantify GMTs. There are two co-primary immunogenicity endpoints for which noninferiority was assessed. The first is the ratio of GMTs of SARS-CoV-2 neutralizing titer against the wild-type virus strains. You can see here the ratio, post-booster dose over post-dose two. Here on the right are the criteria for noninferiority: lower bound of the two-sided 97.5 confidence interval exceeding 0.67 and the point estimate of the GMT ratio of at least 0.8.

The second immunogenicity endpoint that was analyzed for noninferiority was the percentage difference of seroresponse at one month post-booster dose and at one month post-dose two. Seroresponse is defined as at least a four-fold rise and this depends on a baseline measurement that is under the lower limits of quantifications and a postvaccination measure that is at least four times that to be considered a seroresponse.

What was being evaluated here, as prespecified, was the percentage of individuals with a four-fold rise from pre-dose one to one month post-booster dose minus the percentage of those with a four-fold rise from pre-dose one to one month post-dose two. Noninferiority was declared based on the following criterion with the lower bound for the difference in the percentage of seroresponse at these 2 time points of being greater than -10 percent. Here are the immunogenicity analysis populations. Let me see here if I can get the little arrow.

Starting at the top is the 306 individuals who comprised the all available immunogenicity population were those who received BNT162b2 at 30 micrograms. In the process of reaching the evaluable immunogenicity population, 44 were excluded primarily due to important protocol deviation. The number slightly decreased to 234 because of the additional criteria of having no evidence of infection from dose one to one month after booster dose.

In the rectangle on the bottom is the

definition of what was considered "without evidence of infection." Here the slide shows the GMTs against the reference strain in the dose three booster evaluable immunogenicity population without evidence of infection. On the Y axis on a log scale are the GMTs. From left to right, you go from pre-dose one, one month post-dose two, right before booster dose, and then one month post-booster dose.

You can see the trend that has been previously pointed out with the titers increasing dramatically after post-dose two with some waning within six months prior to the booster dose administration and a rise significantly greater than that one month post-booster dose. Here I show the noninferiority analysis based on the GMT ratios against the reference strain. Boxed in blue is the primary analysis population, which are the 210 individuals who are qualified to be in the evaluable immunogenicity population with no evidence of infection.

I'll point you to the right-most column, which is the GMT ratio that we looked at, comparing post-dose

three to post-dose two. The point estimate of 3.29 and a lower bound of 2.76 is clearly above the noninferiority criterion that was mentioned before, which is the point estimate of being greater than or at least 0.8 and a lower bound of greater than 0.67. Here you see the prespecified noninferiority analysis based on seroresponse.

The right-most column shows the endpoint is the difference in seroresponse between one month after booster and one month after dose two. The difference is at 1.5 percent with a lower bound of -0.7 percent. This met the criterion set with respect to the lower bound of being greater than -10 percent. As mentioned previously by Dr. Gruber, we did ask for an alternative or complimentary analysis for which we asked them to define seroresponse using pre-booster rather than pre-dose one to define the seroresponders or the difference in seroresponse between one month after booster dose and one month after dose two.

As you can see here, the numbers are different, but these findings do not challenge the data

from the previous slide which shows that they've achieved noninferior immunogenicity for the two coprimary endpoints. Here I'll go through the exploratory phase one analysis of virus neutralization titers against the Delta variant as well as against the wild type, or reference strain. As previously mentioned, the assay that we used to produce these data come from a 50 percent plaque-reduction neutralization test. This was done in 23 participants against the reference USA strain and the Delta variant.

These titers were assessed in sera one month after dose two and one month after dose three. In the box in the middle of the slide are some considerations, that the PRNT assay is not the same as the validated microneutralization assay for which we have immunogenicity data, which was presented in the preceding slides. It is well accepted and there was (inaudible) but it's not validated and it was used for exploratory purposes.

The relative sensitivity for the two strains currently are unknown. Here are the results. The

columns are divided. You see on the left column Delta variant GMTs, wild type GMTs with confidence intervals. I have presented the 11 18 to 55-year-olds on top of the older adults. You see post-dose two here versus post-booster dose. These numbers have been presented in the previous presentation. This is just arranged slightly differently. You can see that neutralizing titers against the Delta variant and the wild type are present, unmeasurable in both populations or age groups.

You see the difference between post-dose two and post-dose three uniformly across the two strains and across the age group as well. Another post-hoc analysis that we requested from Pfizer had to do with breakthrough infections, particularly those that were detected during the Delta surge. What we asked of Pfizer was to provide numbers of protocol-specified COVID-19 cases that were accrued during early July and end of August in participants 16 years of age and above.

On the left you see we are looking at

participants who completed the two-dose vaccination series early in the study, or the parent study. These refer to individuals who were originally randomized to BNT162b2. Among these almost 19,000 individuals there were 70.3 cases per 1,000 person-years, that's the incidence calculation that Pfizer provided. Three were severe. This was collected over a period of 9.8 months post-dose 2.

On the right you see we're considering the individuals who completed the two-dose vaccination series later in the study, in other words those who were originally randomized to placebo and then crossed over to the active vaccination group. Among these almost 18,000 individuals there was an incidence rate of 51.6 cases per 1,000 person-years. The mean duration was slightly less, as expected, at 4.7 months post-dose 2.

The data here suggests that the incidence of breakthrough infections appear to be higher in those who completed the vaccination series early versus those who completed it later. In order to contextualize this

Delta in incidence, we made the following calculation. Bubble number 1, on the left, you see the ratio that we set at the incidence rate among late vaccinee versus early vaccinee in that came out to 0.73. The purpose of this calculation is to try to translate the relative breakthrough rate to vaccine efficacy.

We took this ratio of 0.73 and, for each of the assumed efficacy values shown in the table below among the placebo crossover group, we calculated the impact of this differential in breakthrough cases on the corresponding efficacy among those who were vaccinated earlier. Let me take you to one. If we assume that the efficacy of the vaccine, let's say, for severe disease in placebo crossover recipients vaccinated later, then the differential in the incidence rate that was determined during the Delta surge would translate to approximately a four percent reduction in vaccine efficacy in those vaccinated earlier.

Continuing on, this is not actually during the Delta surge but pre-Delta surge. If you look at the

numbers, we consider the incidence of COVID-19 among early vaccinees from the evaluable efficacy population before the Delta surge occurred, and the case rate with incidence rate was at 12.6 cases per 1,000 person-years. When we looked at the later vaccinee, the placebo crossovers, in this case before Delta the incidence was actually higher in 43.4 cases per 1,000 person-years.

The takeaway message is the data are complicated and the limitations of the analysis are as follows: the parent study was not designed to assess the relative vaccine efficacy of the crossover group versus the original vaccinees. Therefore, this analysis is exploratory in nature but still we thought would be quite informative or important to consider. In addition, the open-label nature of the booster dose may have introduced confounding factors that included behavioral changes that biased the results and of course, as mentioned previously, there are confounders that we are just not aware of at this time.

Going on to the safety results. As mentioned

previously, the mean length of safety follow-up in the booster recipients in the phase 1 portion and the phase 2/3 portion were basically the same at 2.7 months and 2.6 months, respectively. Here I am showing you the local reactogenicity data across doses. Dose one and dose two data are coming from the reactogenicity subset of vaccinees from the blinded portion or blinded phase of the study with an N of 2899 and 2682.

Comparing this with the reactogenicity of those who received booster, the phase two/tree participants and phase one, and you can see here that injection pain, site pain continues to be the most common local reaction and severity tended to be low with only one case per incidence in the booster recipient. Overall, the data suggests that local reactogenicity does not appear to be enhanced following the booster dose relative to dose two.

I know this is a busy slide. Here are the system reactogenicity-preferred terms that were recorded by eDiary seven days after each dose. Along here, I've ordered the specific adverse reactions in

descending order of frequency. Fatigue is the most common. Here you see the phase two/three dose one recipients, phase two/three dose two recipients, and the booster recipients from the same phase. Fatigue continues to be the most common and severity of fatigue to appear to vary significantly from that observed after dose two.

A similar relationship between all these other commonly recorded systemic adverse reactions can be seen between dose two and dose three. Frequency of fever slightly dipped after the third dose. Use of antipyretics and pain medication were comparable after dose two as compared to after the booster dose. Here we're looking at the systemic reactogenicity profile by age strata. The 289 individuals who submitted eDiary data were 18 to 55. Here, this table only includes the individuals in the 65 to 85 years (audio skip) world age strata, and there are 12. If you look, overall the order of frequency of systemic reactogenicity was about the same.

It's worth pointing out that severe reactions

of any kind in terms of system reactogenicity were not reported among these 12 recipients. Fever was also not reported and the use of antipyretics or pain medication was also less. Now, going on to unsolicited adverse events that were monitored one month post-booster. Here presented in this table are the most common events that occurred in more than two participants, or two or more participants I should say. The one we're pointing out is lymphadenopathy. It occurred in 16 participants with a corresponding frequency of 5.2 percent.

The majority were mild to moderate and they did resolve. All but one is reported to be as ongoing at this time. One, as mentioned previously, was deemed severe due to impact on activity. This occurred two days after the booster dose and resolved over five days. Considering the time period of booster dose to date of cutoff, which is at least 2 months of post-dose three follow-up in the 306 participants, there was one additional AE of acute myocardial infarction reported as an unrelated ASE. This occurred on day 62 post-booster dose and recovered and resolved.

No participants were withdrawn due to adverse events. Among the 306 participants evaluated, there are no cases of anaphylaxis, hypersensitivity, Bell's palsy, appendicitis, or myocarditis/pericarditis. Among the 23 phase 1 booster recipients, there were no AEs that were reported 1 month after booster dose. Finally, I've come to my last slide which is a summary of the data that we reviewed that were submitted to the BLA supplement.

In terms of immunogenicity, success criteria against the reference strain were met for both prespecified coprimary immunogenicity endpoints which were the GMT ratio and the difference in the seroresponse rates among study participants with no evidence of SARS-CoV-2 infection prior to one month after the booster dose. The immunogenicity data to support effectiveness of the booster dose against the Delta variant are limited to exploratory analyses in a small number of participants using an assay, while standardized and with the reference control, is not validated to date.

In terms of the safety data from the 306 phase 2/3 booster recipients, there's no evidence that there is increased reactogenicity relative to dose 2. It is difficult to reach any conclusions about the relative reactogenicity by age as there were only 12 participants, and in the age strata of 65 to 85, the minimum and maximum age range was 65 to 75. Lymphadenopathy was observed more frequently following the booster dose than after the primary series doses.

Worth mentioning, there were no deaths, vaccine-related serious adverse events, or events of myocarditis, pericarditis, anaphylaxis, appendicitis, or Bell's palsy among the 325 booster recipients. I'm done with my portion.

DR. ARNOLD MONTO: Thank you very much. It's time for our break. We will break until the open public hearing begins at 12:30 eastern. We've got a long 13-or-so minute break until the open public hearing. See you back then.

[BREAK]

OPENING PUBLIC HEARING

MR. MICHAEL KAWCZYNSKI: Welcome back to the 167th meeting of the Vaccines and Related Biological Products Advisory Committee Meeting. We will now get started and I'll hand it back over to our acting chair, Dr. Monto.

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

For example, this financial information may

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

DR. PRABHAKARA ATREYA: Okay, good afternoon everyone. This is Prabha Atreya, the Designated Federal Officer for this session who is going to conduct the open public hearing. The first speaker for this session is Dr. Rajesh Gupta. Dr. Gupta, could you please start your presentation please? You have three minutes to go.

DR. RAJESH GUPTA: My name is Rajesh Gupta. Currently, I do consulting for the pharmaceutical industry including vaccine manufactures. I have more than 40 years' experience in development, manufacture, quality control and the regulation of vaccines, both in the industry and regulatory agencies, including CBER,

FDA. There I was the Deputy Division Director on labs team.

Today, I am going to present my views on some aspects about the need for the booster dose of COVID-19 vaccine, based on my experience and understanding of science while working with other vaccines. Next slide please.

Major justification for the booster dose has been waning circulating neutralizing antibodies and incidence of COVID-19 infection in vaccinated individuals a few months after vaccination. Next slide.

A few facts about circulating antibodies. First for most diseases, protective levels of circulating antibodies are not known. When known, for example, tetanus and diphtheria, these are highly variable. Next slide. Secondly, circulating antibodies decline two months after vaccination, but booster dose are not given for most vaccines except for toxin-mediated diseases. Protection against most diseases is not necessarily through maintaining high

levels of circulating antibodies. I'm at slide five now actually. Next slide.

Instead, protection by most vaccine is through rapid deployment of immune system by activation of immune memory by the invading pathogens, except for toxin-mediated diseases, where protection levels are required to be maintained. This is done through periodic boosters every (inaudible) years. The reason is that tetanus and diphtheria toxins are highly potent. Minute doses of these toxins are lethal, but not enough to activate memory. Further, these toxins bind immediately to nerve cells, and are not available to immune cells. Next slide.

Other justifications for a booster have been incidence of COVID-19 infection in vaccinated individuals. However, there is no baseline data for protection against infection for most vaccines. Because unfortunately, clinical trials were not designed to evaluate protection against infection. However, vaccines continue to be highly effective against severe disease. Next slide.

Additionally, there is a risk of original antigenic sin phenomenon after a booster dose. When antibodies to immune-dominant epitopes are made, which get boosted after booster doses with immune memory, vaccinations with a new strain or infection with the new strain hijack the immune system to where the immune response to same epitopes for which antibodies were originally made, leading to no protection against the new strain after disease or vaccination. Next slide.

Finally, booster doses leading to high levels of circulating antibodies may generate escape mutants of SARS-CoV2 virus. So, to finally conclude, based on experience with protection by existing vaccines, booster dose is not justified for general use at this time. It may be justified for immunocompromised or elderly who did not get adequate immune response after initial vaccination. Thank you.

DR. PRABHAKARA ATREYA: Thank you, Dr. Gupta. The next speaker is Mr. Benjamin Newton.

MR. BENJAMIN NEWTON: Thank you. My name is Ben Newton. The question that we must ask every day is

how can we save the most lives. The answer is to approve boosters and follow the American Academy of Pediatrics recommendation to approve pediatric vaccines in August, before school started. Slide two.

The FDA guidelines for vaccine approval stated that vaccines were required to have 50 percent efficacy against symptomatic disease. Further, they require the use of the totality of the scientific evidence, such that if we only use randomized control trial data we violate the FDA guidelines. Slide three.

We saw in April that vaccine efficacy is predicted by neutralizing titers. We have always known this would be the case, but now we had a correlate of protection. Slide four. Also, in April, on the left-hand side, we saw that both variants and time would reduce vaccine efficacy, boosters would be required. On the right side, we saw the 90-day half-life of antibodies. It was clear that we would need boosting in the fall of 2021, at the latest. Slide five.

In June, we saw that the Delta variant and Angola strains had immune escape. The question now

became do we have days or weeks to start boosting? Slide six. In July, we had our answer. We had waited too long to start boosting. Israel published data showing vaccine efficacy had dropped below 50 percent, the FDA minimum standard for people vaccinated five months prior. Israel started boosting days later. We should have too. Slide seven.

Does the FDA have an ethical obligation? Option one is that they don't have an ethical obligation, just an obligation to approve safe and effective medicines. They should approve both boosters and follow the American Academy of Pediatrics recommendation to approve vaccines for children.

Option two is that the FDA has an ethical obligation. Then we must approve pediatric vaccines. We can't randomize pediatric trials 50/50 because that would be unethical, but there are 50 million American children who are not free to be vaccinated today. We should approve lower doses. I and others have explained to the FDA how to optimize dosing to save lives. If you care to watch a longform explanation,

you can check out the YouTube video here. In addition, we should approve boosters. If you don't approve boosters, then only people with good doctors can be boosted. Slide eight.

The FDA had a reputation to protect. The FDA built its reputation by saving lives with thalidomide. With COVID, the FDA has squandered its reputation. The FDA lagged other regulators, often by months, in approving vaccines and diagnostic tests. Randomized control trials became unethical the instant we knew, or importantly should have known, that vaccines worked. If you fail to look at data it does not mean the data doesn't exist.

It is important to note that developing a vaccine took two days, we are quickly approaching two years. When will all Americans be free to be vaccinated? Slide nine. This is not the last pandemic or variant. The FDA must determine how to approve vaccines as fast as viruses spread. Boosting with wild type vaccines increases the chance that vaccine efficacy will drop precipitously. I thank you for your

time and service.

DR. PRABHAKARA ATREYA: Thank you, Mr. Newton. The next speaker is Dr. Jessica Rose.

DR. JESSICA ROSE: My name is Dr. Jessica Rose, and I'm a viral immunologist and computational biologist. I've taken it upon myself to become a VAERS analyst who organizes data into comprehensive figures to convey information to the public in both published work and video mediums.

Safety and efficacy are the cornerstones of the development and administration of biological products meant for human use. Risk is the number of the probability of an adverse event occurring and the severity of it results in harm to health of individuals in a defined population. Safety is a judgement of the acceptability of its risk in a specified situation. Efficacy is the probability of benefit to individuals in a defined population from a medical technology. Refer to slide one.

This is a bar graph that shows the past 10 years of VAERS data plotted against the total number of

adverse event reports for all vaccines for the years 2011 through 2020. And for COVID-associated product only for 2021. The left side graph represents all adverse event reports, and the right side represents all death adverse event reports. There's been over 1,000 percent increase in the total number of adverse events for 2021, and we are not done with 2021. This is highly anomalous on both fronts.

These increased reporting rates are not due to increase rates in injections and not seen due to simulated reporting. This has been shown using a comparative analysis of influenza data. The onus is on the public health officials: the FDA, the CDC and policy makers to answer to these anomalies and acknowledge the clear risk signals emerging from VAERS data, and to confront the issue of COVID injectable products use risks that, in my opinion, outweigh any potential benefit associated with these products. Especially for children. Slide two.

This is a time series plot that shows the total cumulative number of cardiovascular immunological

and neurological adverse events for 2021 associated with COVID products. Unaccumulated absolute counts are normalized for the total number of fully-injected individuals in the U.S. We can see that 1 in 660 individuals are succumbing to and reporting immunological adverse events associated with the COVID products. The underreporting factor is not considered here. Slide three.

This is a phylogenetic tree showing the emergence of the Alpha and Delta variants of COVID-19 over time. The emergence of both of these variants, and their subsequent clustering, arose in very close temporal proximity to the rollout of the COVID products in Israel. The surrounding data from the Ministry of Health and overwhelming data reveal that 98.1 (audio interference). Oh my god, sorry about that.

Israel is one of the most injected countries, and it appears from this data that this represents a clear failure of these products to provide protective immunity against emergent variants and to prevent transmission regardless of how many additional shots

administered. This begs the question as to whether these injection rollouts are driving the emergence of the new variants. There's a clear and present danger of the emergence of variants of concern if we continue with these alleged booster shots. Thank you.

DR. PRABHAKARA ATREYA: Thank you, Dr. Rose. Next speaker is Dr. Retsef Levi. Dr. Levi.

DR. RETSEF LEVI: Good afternoon everybody. Good afternoon everybody, my name is Retsef Levi. I hope you can see my personal title slide labeled as slide A on the bottom right. I'm on the faculty of the MIT Sloane School of Management. I have no conflict of interest to disclose today. And my presentation represents only my individual opinions and does not reflect in any way on the positions of MIT. Next is slide B.

Pfizer's request for the approval of the boosters is partially based on the so-called study conducted in Israel. It is important to understand that the booster vaccination campaign in Israel was anything but a carefully designed study. In a matter

of less than six weeks, Israel moved from its initial intention to vaccinate the over 60 population to vaccinating anyone above the age of 12, and it is now about to mandate booster vaccination for anyone to maintain green passport status. This does not allow any reliable learnings, definitely not in such a short amount of time. And please understand that the adverse events surveillant system in Israel is truly dysfunctional, particularly around the booster deployment. I know from personal experience that the Ministry of Health in Israel does not address appropriately major concerning safety signals. Next, slide C.

This leaves us with the question, what drove this massive booster deployment? Next, slide D. Trying to reach vaccine-induced herd immunity by reducing transmission rates will be consistent with the stated goal of the agreement that Israel signed with Pfizer as you can see on slide D on the left-hand side. The problem is that by now we already know, from mounting evidence, that reaching herd immunity based on

the current vaccine does not seem like a feasible or realistic goal. Not surprisingly, as you can see on the right-hand side of slide D, Israel continues to have among the highest infection rates per capita in the world. Next, slide E.

You all listened to a presentation of the Israeli Ministry of Health that praises the efficacy of the boosters. I would like to question this premature celebration and remind you that similar statements were made just six months ago around February on the two initial doses. Note on slide E, on the right-hand side, that COVID-19 deaths in Israel, in spite of all of the boosters, are on the rise. Whereas, in other countries, including many States in the U.S., they seem to be on downward trend at the moment.

The data from Israel also highlights that the main risk of serious COVID-19 outcomes is focused to large extents among the completely unvaccinated population, and almost entirely in the over 61. On the left-hand side of slide E, you can also see data from Phase I in a research paper by the Ministry of Health

in Israel that suggests that the benefit from the booster, compared to the prior two doses in preventing serious illness, might be much more limited than desired. There's much more to say about the problems of the current booster efficacy study. Next, slide F.

Let me conclude by stressing how important it is to transition from emergency strategies to long-term ones. Slide F outlines five important considerations in doing so. They are self-explanatory. I hope you will hold off of approving this booster for broad use, at least until such a strategy is developed. Thank you for your attention.

DR. PRABHAKARA ATREYA: Thank you, Dr. Levi. The next speaker is Dr. Joseph Fraiman.

DR. JOSEPH FRAIMAN: Hello. Please if you can go to my first slide? Hello, my name's Dr. Joseph Fraiman, no conflicts to declare. I'm an emergency physician educated at Cornell Medical School. My residency was Charity Hospital in New Orleans, and I've been working in this region since.

Where I work, over 65 percent of the

population are not vaccinated. I'm here today to ask for help. For those working the frontline to help us reduce vaccine hesitancy. For this, we need larger trials that demonstrate the vaccine reduce hospitalization without finding evidence of serious harm. I know many think the vaccine hesitants are dumb or just misinformed. That's not at all what I've seen. In fact, typically, independent of education level, the vaccine hesitant I've met in the ER are more familiar with vaccine studies and more aware of their own COVID risk than the vaccinated. Next slide please.

For example, many of my nurses have refused the vaccine, despite having seen COVID-19 cause more death and devastation than most people have. I asked them why refuse the vaccine? They tell me while they've seen the first-hand dangers of COVID in the elderly, the obese, diabetics, they think their risk is low. They're not wrong. Next slide please.

One nurse showed me this Oxford Risk Calculator. A 30-year-old female has about a 1 in 7,000 chance of catching COVID and being hospitalized

over 90 days. She asked me, can I assure her that the studies found her risk of serious harm from the vaccine is lower than her risk of hospitalization? The truth is, I can't. Our trials weren't big enough. They weren't big enough to identify the vaccines cause myocarditis, yet now we know they do. Next slide please.

A recent observational study suggests the risk of vaccine-induced myocarditis in young males is higher than their risk of hospitalization from COVID, is this true? We don't know. It's based on observational data. To know it's not true, we need a large trial that proves that vaccines reduce hospitalization more than they cause myocarditis in this age group. Next slide please.

The former FDA commissioner said the original premise of the vaccine was to reduce death and hospitalizations. That was the data that came out of the initial clinical trials, except, as you all know very well, unfortunately so did my nurse, the initial clinical trials did find a reduction in death or

hospitalization, likely because they were inadequately powered. Yet, the former commissioner is correct, that the initial trials should have been powered to find a reduction in hospitalization. Next slide please.

We need your help on the frontlines to stop vaccine hesitancy. Demand the booster trials are large enough to find a reduction in hospitalization. Without this data, we, the medical establishment, cannot confidently call out anti-COVID vaccine activists who publicly claim the vaccines harm more than they save, especially in the young and healthy. The fact that we do not have the clinical evidence to say these activists are wrong should terrify us all. Thank you. Next slide.

DR. PRABHAKARA ATREYA: Thank you, Dr. Fraiman. Our next speaker is Mr. Steve Kirsch.

MR. STEVE KIRSCH: Hi, I'm Steve Kirsch, I'm Executive Director of the COVID-19 Early Treatment Fund. I have no conflicts. Advance to slide number four with the elephant.

I'm going to focus my remarks today on the

elephant in the room that nobody likes to talk about, that the vaccines kill more people than they save. Today we focus almost exclusively on COVID death saves and vaccine efficacy because we were lead to believe that the vaccines are perfectly safe. But this is simply not true. For example, there are four times as many heart attacks in the treatment group in the Pfizer six month trial report. That wasn't bad luck. Theirs shows heart attacks happen 71 times more often, following these vaccines, compared to any other vaccine. In all, 20 people died who got the drug, 14 died who got the placebo. Few people notice that. If the net all-cause mortality from the vaccines is negative, vaccines, boosters and mandates are all nonsensical. This is the case today.

Death rates -- slide number seven. Advance to the number seven. This shows that the all-cause death:life ratio in three cases. Only the VAERS numbers are statistically significant, but the other numbers are troubling. Even if the vaccines had 100 percent protection, it still means we kill two people

to save one life. Four experts did analyses using completely different, non-U.S. data sources, and all of them came up with approximately the same number of excess vaccine-related deaths, about 411 deaths per million doses. That translates into 150,000 people have died. Next slide would be slide number 11. The nursing home.

Now the real numbers confirm that we kill more than we save. And I would love everyone to look at these Israel Ministry of Health data on the 90-plus-year-olds where we went from a 94.4 percent vaccinated group to 82.9 percent vaccinated in the last four months. In the most optimistic scenario, it means that 50 percent of the vaccinated people died and zero percent of unvaccinated people died. Unless you can explain that to the American public, you cannot approve the boosters. Slide number 16 please. Myocarditis.

The paper just posted yesterday on Med Archive, entitled *mRNA COVID-19 Vaccination and Development of CMR-Confirmed Myopericarditis*, shows that the myopericarditis risk was 1 in 1,000, and

that's an overall age range from 18 to 65, mean age of 33. It is not inconsistent with what the VAERS shows. Next slide would be slide number 18, gaming of the trial.

It's pretty clear that the Pfizer trial results were gamed. It's statistically impossible for protocol violations be five times higher in the treatment group. Why hasn't this been investigated? Slide number 19. Maddie de Garay was 12 when she enrolled in the Pfizer Phase III trial for kids, now she's paralyzed for life. It wasn't reported in the Pfizer results. I told Janet Woodcock there was no investigation. Please tell us why this fraud was not investigated.

And, finally, slide number 20, please. Early treatments are a much better alternative to boosters. The proof is that in Israel, cases are at an all-time high. In India, Uttar Pradesh is now COVID-19 free as of today. Almost nobody there is vaccinated. Thank you.

DR. PRABHAKARA ATREYA: Thank you. The next

speaker is Mr. David Wiseman.

MR. DAVID WISEMAN: Thank you, Dr. Monto, please see our written comments. Next slide, B, for disclosures, and next slide, slide C. With this *Lancet* paper by FDA vaccine officials we find ourselves agreeing with them, but for different reasons. We have an unclear need with unclear motivation, significant safety concerns, poor evidence of sustained booster efficacy and wrong priorities. So while FDA and Pfizer can't agree about waning efficacy -- let's go to next slide, D. We saw recently CDCs apparent withholding of key data from ACIP prior to recommending the Pfizer vaccine and revealing that the primary driver for approving Comirnaty was to overcome hesitancy through regulatory misdirection. We agree with others that this has become politicized. Next slide, E.

Pfizer's booster evidence today is weak. They are small studies in mostly younger subjects. They are short-term, there is no randomized control. There are no clinical outcome data, only serology. Inadequate safety given this is a gene therapy product. Where are

the data from the 10,000 patient study? Next slide, F. If FDA cannot assure us of the safety of two doses, how can they assure us of three? We see strong signals for death, myocardial infarction and coagulopathy that need transparent investigation. Next slide, G.

We can find three potential cause of vaccine associated deaths. Note the second who are among vaccinees. Next slide, H. Daily cases in Israel increase upon booster rollout compared with the same period last year. Please note the correct rollout is July the 1st of the 130 number. The Israel booster data presented today has matching sensory bias seen in related studies. Non-comparable populations, possible clustering bias, inadequate accounting for early vaccine effects and a short follow-up in mainly older people. Next slide, I.

Others show unexplained Israeli deaths lock-stepping with booster rollout. This looks like the second (audio skip) deaths we've said before in vaccinees rejected by *New England Journal of Medicine* in February. Next slide, J. Other safety concerns,

not voiced in the label, are revealed in studies funded offline by NIH for menstrual disorders. Next slide, K. And offline, by CDC, in a disturbing revelation of an urgent need to monitor safety in pregnancy. Put this in the label.

Next slide, L. Long-term safety, no cancer studies were performed. Moderna said its vaccine was a gene therapy product. Why is the FDA not requiring 5 to 15 year cancer and other studies per their gene therapy guidance? Next slide, M. We propose the term pCoVS to describe the wide spectrum events being reported. Next slide, N.

We are running out of options, vaccine hesitancy won't be solved by bullying or coercion. Address safety, show convincing booster efficacy, revisit repurpose drugs. Next slide, O. We reverse the findings of flawed landmark studies that have misguided policy. Journals refuse to correct these defects and Dr. Rubin's seat on this committee is a conflict. Next slide, P. This is what has to be done. Thank you very much.

DR. PRABHAKARA ATREYA: Thank you. The next speaker is Mr. Kermit Kubitz.

MR. KERMIT KUBITZ: Hello. My name is Kermit Kubitz. I have reviewed this presentation with other friends from CalTech. I have previously commented to the ACIP in December in support of EUA for the Pfizer vaccine. At that time I said my only conflicts were elderly relatives who needed the vaccine yesterday. Since then, two of those three relatives have received the vaccine. One with rheumatoid arthritis has received a booster with no adverse effects. Next slide.

The table of booster pros and cons. Reasons against boosters are lack of need in view of current efficacy, risks, confidence and global vaccine equity. However, I believe there are substantial reasons for boosters, including normal vaccination protocol involves a delay of months. Boosters may limit infectious cases in large gatherings and global vaccine supply will be from a more conventional vaccine not requiring uninterrupted cold chain. Next slide.

Balancing booster pros and cons. Breakthrough infections, although milder, are occurring. Vaccine hesitancy is generally not rationally based. A phased booster approach would allow greater global vaccine availability and the United States could boost international vaccine supply by funding new lower cost vaccines, such as Biological E. Next slide. Country approaches to booster vaccinations support boosters: Canada, Italy, Greece, Britain, China and France. Next slide.

Conclusions. As my friend Chuck Wolf has commented, it's important to plan for boosters now even if not everyone will receive a booster. There are three priorities: one, the unvaccinated, two, children 6 to 11 and three, boosters for other people. There are outbreaks in schools that have nearly shut down schools in Raleigh, North Carolina. Booster vaccinations should be offered beginning with age priority, either 65 and older or 50 and older. Booster vaccination may offset, "social hesitancy" of those who fear social interactions within anyone else and are thus isolated.

But we should plan for boosters and the commission should promptly approve booster vaccination while dealing with the other priorities, the unvaccinated and school children. Thank you very much for your time.

DR. PRABHAKARA ATREYA: Thank you, Mr. Kubitz. The next speaker is Dr. Peter Doshi.

DR. PETER DOSHI: Hi, I'm Peter Doshi, and thanks for the opportunity to speak. Hopefully, you can see my title slide with my financial disclosers. For identification purposes, I'm on the faculty of the University of Maryland and an editor at the BMJ. I have no relevant conflicts of interest. Next slide please, which is labeled slide A.

I want to start off by asking a question, just what problem is this third dose aiming to solve? If we have a pandemic of the unvaccinated, as the public health officials have repeatedly stated, why would a "fully vaccinated person" need a third dose? Next slide B, please.

The briefing document suggests the rationale for boosters is waning immunity, but the lowest vaccine

efficacy figure mentioned is 83.7 percent. And last month, FDA approved Pfizer's vaccine stating that efficacy against symptomatic COVID is 91 percent. Sure, a third dose might nudge up efficacy numbers, but so too might a fourth dose and a fifth dose. The thing is the two-dose regiment efficacy numbers are already way higher than the 50 percent bar that FDA set in June last year for an approvable vaccine. Before contemplating the licensure of dose three, shouldn't FDA first require evidence that the two dose regiment no longer meets the efficacy bar the agency just weeks ago said it met? If vaccine efficacy is now below 50 percent, let's see the data. Next slide C, please.

Let's discuss safety. When discussions about a third dose began in July, CDC Deputy Director, Dr. Jay Butler, said it was vital to find out if the third dose increased adverse reactions, particularly severe ones. Unfortunately, we're still in the dark. Pfizer's booster application reports on just 329 people with no control data. Now there is a Pfizer ongoing placebo controlled randomized trial of boosters in

10,000 not discussed in the briefing documents. But this trial is unlikely to satisfactorily characterize booster safety.

First, the trial is too small and the enrollment is limited to healthy participants. Second, we really need to know how safe boosters are in people who already had bad reactions to dose one or two, but such people are obviously less likely to volunteer to participate in this trial. So we won't have the data to answer the question. Yet, if the booster is approved, such people will surely be mandated to receive a third dose. Final slide D, please.

I'll end with a question. Last week, three medical licensing boards said that they could revoke doctors medical licenses for providing COVID vaccine misinformation. I'm worried about the chilling effects here. There are clearly many remaining unknowns and science is all about probing unknowns. But in the present super-charged climate -- and I'll point out that multiple members of this committee are certified by these boards -- I want to ask FDA, what is the FDA

doing to ensure that those advising it are able to speak freely without fear of reprisal? Thank you for your attention.

DR. PRABHAKARA ATREYA: Thank you, Dr. Doshi. The next speaker is Dr. Michael Carome.

DR. MICHAEL CAROME: Hello, I'm Dr. Michael Carome, Director of Public Citizen's Health Research Group. I have no financial conflicts of interest. Public Citizens supported the Emergency Use Authorization and subsequent approval of the Pfizer-BioNTech COVID-19 vaccine because clinical trial data demonstrated the vaccine was highly effective and generally safe. However, Pfizer and BioNTech have failed to provide sufficient evidence to assess the risk/benefit profile of a booster, or third dose of their COVID-19 vaccine, in individuals aged 16 or older in the general population. In particular, there is a lack of data on the effectiveness and its duration of booster vaccination in preventing important COVID-19 related outcomes. That is, serious illness resulting in hospitalization or death in individuals aged 16 and

older in the general population, and safety data for booster vaccination is very limited.

Importantly, observational studies indicate that the primary series of the Pfizer-BioNTech vaccine still affords robust protection against severe COVID-19 disease and death in the U.S. We agree with the following assessment and conclusions offered by doctors Gruber and Krause, and other experts, in their viewpoint article published in *The Lancet* this week. Quote, "Current evidence does not appear to show a need for boosting in the general population in which efficacy against severe disease remains high. The limited supply of COVID-19 vaccines will save the most lives if made available to people who are at appreciable risk of serious disease and have not yet received any vaccine. Even if some gain can ultimately be obtained from boosting, it will not outweigh the benefits of providing initial protection to the unvaccinated. If vaccines are deployed where they would do the most good, they would hasten the end of the pandemic by inhibiting further evolution of

variants." End quote.

Finally, any move to widespread distribution of COVID-19 vaccine boosters in the U.S. would make it even more ethically imperative that the U.S. government move to ramp up global vaccine manufacturing so that everyone on the planet can be vaccinated. The world currently is suffering an artificial scarcity of high quality COVID-19 vaccines because governments are permitting drug corporations to maintain monopolies. While the U.S. has been planning its booster vaccination campaign, the vast majority of people in low and middle income countries have no access to any COVID-19 vaccine, let alone the highly effective mRNA vaccines.

If the U.S. is to proceed with COVID-19 vaccine boosters, we take on a special, greater obligation to do everything in our power to get as many vaccine doses as possible, as quickly as possible, to people in low and middle income countries. And especially to invest immediately in an expanded manufacturing to create an adequate supply to vaccinate

the entire world. Thank you for your attention.

DR. PRABHAKARA ATREYA: Thank you, Dr. Carome. The next speaker is Kim Witczak.

MS. KIM WITCZAK: Hi, my name is Kim Witczak with Woody Matters, a drug safety organization started after the death of my husband. I'm also on the board of directors of USA Patient Network and have no conflicts of interest.

It seems we are here today to discuss Pfizer's application to redefine the meaning of fully vaccinated from two to three doses. From the beginning of the pandemic, the goalposts keep changing. It makes you wonder if the current vaccination strategy is working. When looking at the submitted data, is just over 300 people with only 12 of them over age 65, the highest risk group, sufficient enough to warrant approval for boosters? If the FDA approves this, we will take what we've learned on just 300 people and then give it -- no, more like mandate it -- to hundreds of millions of people. This is beyond preposterous.

While I am no vaccinologist, it would seem

logical that dose three would have an increase in immune response over two, four doses over three, five over four and so on. At what point will enough be enough? At the end of the day, can we really vaccinate our way out? While boosters may be good for business, let's be real, these mRNA vaccines were never designed to stop transmission or eradicate the virus. These vaccines are not the same as those being used to eradicate polio or smallpox.

I have to wonder why we chose to go down the vaccine path first versus focusing on treating those with the COVID diagnosis before it was too late or ended up in the hospital or worse yet, dead. And, also, we haven't heard any discussion from our national leadership on the role natural immunity plays. Instead, NIH, CDC, FDA and the White House have told Americans that vaccines are superior to our innate immune systems and beat out any natural acquired immunity. Let's take a step back and look at the bigger picture.

First, our government incentivized -- more

like bribed -- the public to get these shots. Then we were told about the possible need for boosters while shaming and blaming the unvaccinated. Now the government is forcing them with mandates. Is there a reason why we want everyone to be vaccinated? Is it so adverse events can't be distinguished between vaccine and the virus? Or is to help masquerade the waning effectiveness of vaccines and blame the new variants, when it may just be the mutating virus escaping leaky vaccines.

Politics and fear seem to be in the driver's seat. Facts around data and science can no longer be questioned or openly debated without being discredited or labeled as misinformation. Just look at what the professional medical societies are collectively doing, threatening doctors with losing their medical license if they deviate from the official protocol or narrative established by CDC and public officials like Dr. Fauci.

People are not able to talk about their negative experiences without being dismissed, harassed or being called an antivaxxer. Just look at what

happened to rapper Nicki Minaj this week. People came out and attacked her for telling her families story and voicing an opinion. We are walking a slippery slope when regular people, celebrities, doctors and scientists are silenced or, worse yet, censored.

Finally, I would be remiss if I failed to mention the hundreds of thousands of people who paid the high price by doing the right thing for the greater good. Their lives have been forever changed. I don't have enough time to begin to touch on the currently reported safety issues impacting tens of thousands, including children and young adults, and all the future safety issues not yet realized. Ladies and gentlemen, we are part of the largest pharmaceutical experiment ever conducted on humankind. Thank you so much and I appreciate your deliberation.

DR. PRABHAKARA ATREYA: Thank you, Ms. Witczak. The next speaker, Paul Alexander, we could not connect him, so we'll try it later. So we move on to the next speaker, Ms. Lynda Dee.

MS. LYNDA DEE: Hi, yes, my name is Lynda Dee.

I have no conflicts. I have been a community rep for many CEDR antiviral advisory committee hearings. Emphasis on the unvaccinated and international vaccine donations from the U.S. issues are misplaced. FDA does not have the power to increase international vaccine donations or create policies to promote increased vaccinations at home or abroad.

We are here because there are differing opinions on whether there is sufficient data to support licensure of a third dose of BNT162b2 for people 16 and older. The sponsor is relying on data from a number of sources that show activity wanes between six and eight months after the second dose. It also suggests breakthrough cases were caused by waning effectiveness, not the Delta variant. Sponsors also conducted a sub-study within their registrational study that eventually established safety in 306 participants 18 to 55. I think the Israeli safety data was helpful, even if it was in mostly older people.

The third 162b2 dose was found to be as well-tolerated as the second dose and elicited responses to

wild type virus not inferior to the second dose response. The sponsor believes the FDA development guidance permits these data to be extrapolated to include individuals 16 and 17 as well as people over 55. Has the sponsor provided sufficient data from adequate clinical trials to justify their request for licensure?

Reasonable people strongly disagree as is evidenced by the different positions taken in recent *New England Journal* and *Lancet* articles. I've been an AIDs activist for some 35 years. I understand only too well the need for access, but I have learned the importance of evidence-based medicine the hard way. We all rely on the FDA to ensure that interventions are safe and effective. If you do not believe the data are sufficient to justify the full approval, please consider the innovative practical solution of accelerated approval, which we've used in the HIV arena for many years.

Which also permits -- yeah and is also permitted in some circumstances for vaccines, according

to the General Principles for the Development of Vaccines to Protect Against Global Infectious Diseases guidance, even though this guidance addresses international issues.

Accelerated approval will permit access and requires the sponsor to conduct or complete at least one adequate, well-controlled conformational trial before full approval is granted. This option should be considered as it provides the best solution for both the access and additional data dilemma questions presented here. Thank you.

DR. PRABHAKARA ATREYA: Thank you, Ms. Dee. The next speaker is Dr. Meg Seymour.

DR. MEG SEYMOUR: Thank you for the opportunity to speak today on behalf of the National Center for Health Research. I am Dr. Meg Seymour, a senior fellow at the Center. We analyze scientific data to provide objective health information to patients, health professionals and policymakers. We do not accept funding from drug and medical device companies, so I have no conflicts of interest.

Today you're asked to discuss whether the data presented support the safety and effectiveness of a booster dose of the COVID-19 vaccine, and if so, for whom. I will focus on the safety sample data discussed in the FDAs briefing document. The total safety sample is very small, only 329 patients. Even more important, the sample is not representative of the people who will want the booster.

There are safety data on only 12 patients aged 65 and over, even though people over 65 are considered a priority group for a booster due to weaker immunity. Twelve people over 65 is much too small to draw conclusions about safety, and it's obviously not large enough to have any confidence in the claim that adverse events from booster doses are less common in those 65 and over. In addition, there is zero patients ages 16 and 17, and safety for this population is being extrapolated based on safety for those 18 and over. Data should be collected for any population that the boosters would be approved for rather than extrapolating pediatric safety from adult safety data.

Unfortunately, the size of the sample is not the only problem with the safety data. A median of 2.6 months is not enough time for assessing the safety of the booster. In addition, we agree with the FDA that it is unknown whether there'll be an increased risk of myocarditis, pericarditis or other adverse reactions after a booster dose.

We all know that COVID can be deadly, but the efficacy of a booster compared to no booster is not well-established since the placebo control group is missing in addition to uncontrolled variables that could influence the diagnosis of COVID for those with boosters and those vaccinated without boosters. Assurance that the benefits outweigh the risks should be gathered before approving booster vaccines. Otherwise, the potential risks may become obvious only after large numbers of the general population have received boosters, and the benefits of boosters may be much less than expected.

FDA decisions should be based on proof of the safety and effectiveness of a medical product before

the product's widely distributed. To approve a booster without adequate safety or efficacy data undermines the integrity of the FDA. It is unfortunate that the White House announced the need for and availability of boosters prior to FDAs assessment of the data. We know numerous people who have already received booster doses by merely asking their doctors or local pharmacies for a third dose.

We all want to get the COVID-19 pandemic under control and protect as many people as possible, which is exactly why it is so important to carefully and scientifically assess the safety and effectiveness of COVID-19 booster vaccines. The data provided for this meeting do not allow us to draw confident conclusions, and a premature decision will make it impossible to do the research necessary to draw scientific conclusions. Thank you.

DR. PRABHAKARA ATREYA: Thank you, Dr. Seymour. The next speaker is Ms. Kathleen Cameron.

MS. KATHLEEN CAMERON: Good afternoon. My name is Kathleen Cameron. I'm a pharmacist, public

healthcare professional and Senior Director of the Center for Healthy Aging at the National Council on Aging, or NCOA. I have no conflicts to declare.

I appreciate the opportunity to provide comments today on behalf of NCOA, older adults, their family members and caregivers and organizations that serve them. NCOA is a respected national leader and trusted partner to help people aged 60 plus live with health and financial security. We believe every person deserves to age well.

Vaccines are a vital part of aging well and NCOA is committed to ensuring older adults have accurate and timely information about them to avoid confusion when making decisions. We also advocate for access to approve vaccines using public benefits for which older adults are entitled. Older adults have been disproportionally impacted by the Coronavirus pandemic. Those 65 and over represent 13 percent of COVID-19 cases, yet account for nearly 80 percent of the deaths. COVID-19 also is having a disproportional impact on communities of color, who have had always had

to face health disparities such as higher rates of chronic conditions, income inequality and inadequate access to quality healthcare. The older adults in these communities have historically fared even worse.

Further, we now know that older vaccinated people are most vulnerable to illness and hospitalization after a breakthrough infection. As the CDC recently reported, this may be due in part to waning immunity that is most significant in people aged 65 and up, who are at greatest risk for hospitalization and death from COVID-19. NCOA commends VRBPAC's diligent and rigorous work as our country continues to face the evolving COVID-19 pandemic. Every day brings new knowledge about the virus, the effectiveness of COVID-19 vaccines and the potential need for vaccine boosters as discussed during this meeting today.

The impact of COVID-19 pandemic on older adults has been tremendous and we want to do all we can to protect older adults as well as healthcare and long-term care workers. As we continue to learn more about the long-term effectives of COVID-19 vaccines, we are

counting on the FDA to conduct gold standard reviews and to develop appropriate recommendations as you have done so well for many years. We ask that you carefully examine all available data on safety and effectiveness of COVID-19 vaccines over time among various population groups, especially older adults who are most vulnerable. And make your decision about booster shots as expeditiously as possible. Thank you again for the opportunity to provide comments, and we welcome further discussion and involvement as decisions are being made. Thank you.

DR. PRABHAKARA ATREYA: Thank you so much. The next speaker is Ms. Beth Battaglino.

MS. BETH BATTAGLINO: Hi. Thank you for allowing me time today to present on behalf of Healthy Women. I'm Beth Battaglino, President and CEO of Healthy Women. We were founded in 1988. And Healthy Women is the leading nonprofit women's health information source with the mission of educating women, ages 35 to 64 of age, to make informed health choices.

Throughout the years we have informed

consumers and healthcare providers about the advances in women's health. From the latest information on diseases and conditions to various milestones pertaining to access to care. We ensure that women have accurate, balanced, evidence-based information so that they can make informed decisions in partnerships with their healthcare providers. We also educate our audience regarding innovations in research and science, as well as changes in policy that affect women's access to treatments and care, so that women are prepared to self-advocate for better health outcomes.

We know the importance of the process as we continue to educate our audience that the COVID-19 vaccine, like other drugs, are only approved following an established, gold standard review process. COVID-19 vaccine development follows the FDA review process that includes research, multi-stage clinical trials, robust regulatory reviews and approvals and ongoing safety monitoring.

We also know that data on booster shots for all three vaccines continues to be studied, and we

anticipate more information from the FDA and the CDC very soon. Healthy Women will be ready to share out medically-vetted, science-based research information on the booster shot with our audience of over 1.5 million women. Thank you.

DR. PRABHAKARA ATREYA: Thank you, Ms. Battaglino. The next speaker is Brian Hujdich. Sorry if I didn't say your name right.

MR. BRIAN HUJDICH: Thank you for the opportunity for health advocates to provide direct feedback. I have no financial conflicts to disclose. I'm Brian Hujdich, Executive Director of HealthHIV, a national nonprofit organization based in Washington, DC. We advocate for communities impacted and affected by HIV.

Today I'm speaking to you as a health services advocate in an effort to get us all one step ahead of breakthrough infections among fully vaccinated people. While data clearly show that COVID-19 vaccines are highly effective against current strains, preliminary data also indicate that protection against infection

overall appears to be waning. And that concerns us because it puts the populations we serve at even further risk for infection based on the point and time immunity of the general population.

COVID-19 is a serious and potentially fatal and life-threatening virus. Not just for those most at risk, like the immunocompromised and immunosuppressed, but for everyday Americans, especially front-facing, service sector, minority communities and marginalized populations in geographies with the highest viral load concentration. Often a result of vaccine hesitancy or opposition. Not surprisingly, breakthrough infections appear to be more common among those with weakened immune systems. And, according to data presented at a CDC advisory committee on immunization practices, immunocompromised patients represent 44 percent of hospitalized COVID-19 breakthrough cases, even though they only make up about 2.7 percent of the total population.

As part of this data lookback, the FDA evaluated the science on the use of a third dose of the

Pfizer or Moderna vaccines in people with compromised immune systems, and they rightly determined that a third vaccine dose may protect them and others around them. In fact, they interpreted the findings to state that targeted policies, like the booster shot being proposed today, need to evolve as both science and risk evolve. It confirms that people with underlying conditions, like advanced HIV, cancer, organ transplant, hemodialysis and those on immunosuppressive therapies, are seen as a significant risk for poor outcomes from COVID-19.

In essence, it highlights the need for our populations to stay as healthy as possible, but it also depends on the health of those around us. Fortunately, the vast majority of breakthrough infections are typically mild, but we are discussing the rationale for a booster shot in efforts to prevent the clock from winding backwards. We encourage the advisory committee to recommend booster shots for people aged 16 and above, just as you did to protect people living with HIV. Thank you.

DR. PRABHAKARA ATREYA: Thank you so much. The next speaker is Dr. Paul Alexander.

DR. PAUL ALEXANDER: Hi, thank you very much. I got cut off earlier, but thanks for patching me back on, that's good work by you guys.

Look, I wanted to get into this by saying my background is in evidence-based medicine, clinical epidemiologist. I'm very interested in the safety and efficacy of this vaccine. I'm following some very good presentations so far. Look, we want these vaccines to work as Americans and as global populations. So I think the message has to be that we're not coming at the FDA, or we're not coming at the CDC, trying to raise issues and just -- can you hear me?

MR. MICHAEL KAWCZYNSKI: Yes, we can hear you.

DR. PAUL ALEXANDER: Yes. It's not that we want to raise issues and concerns, but here's the issue, we want it to work. But when we look at the surveillance coming out of the VAERS right now, CDC, it captures 1 to 10 percent by our study of the published literature. (Audio skip) adverse events. And that is

very sub-optimal because it doesn't give a proper capture of the burden. So we really do not know what the adverse events and the deaths are.

So we want proper safety monitoring boards, we want proper ethics committees following up on these vaccines. We are calling for critical event committees, but we do not seem to know whether they exist. So we want the FDA to get on top of these vaccine developers -- and the CDC -- and put this in place for the safety of Americans. And it's a simple issue, you are giving us the vaccines, and this is what we have been clamoring for.

If you have an investigation of a vaccine with 1,000 samples, you put 500 in each arm and you follow that for one year; versus, you have another study of 100,000 people and you follow that for two months. And the safety events that we are looking for, the safety signals, happens at about five to six months. How could that large a sample detect them? And that's the issue.

We are calling for longer term studies, larger

sample size, but longer term. We need the medium and long-term studies to best assess the safety and efficacy. Particularly safety. Particularly when you talk about putting this vaccines in our children's arms. We currently do not have this safety data. We actually do not, and for anyone at the CDC, anyone at the NIH and anyone at the FDA that claims so, that is being disingenuous to the public.

Now I wanted to end by saying this, I looked at a study this morning by Chen (phonetic) on testicular infection post CoV, SARS-CoV-2 virus. That means that there is an issue. And we're extrapolating based on Japanese data that look at the lipid nanoparticles in the mRNA that were accumulating in the tissue in the rat model. Yes, it's a rat model, but we have to extrapolate to humans. That showed that the lipid nanoparticles, the constituency of the vaccine is accumulating in the ovaries, in the testes, in the spleen, in the adrenals, et cetera.

So when somebody like Nicki Minaj -- I have to invoke this -- makes that statement, that's not a joke.

People want to make this a joke and parody it, et cetera, but this is a very, very serious consideration. Because we even have animal data that shows us that there is a drop in fertility in the animal model.

So we need this properly investigated. The public needs this answer properly. And I want to end by saying this, under no condition -- none, zero -- based on the evidence today, must children be indicated for these vaccines. There is no risk to children. No -- statistical, zero, in terms of spreading and in terms of getting serious illness or dying from this. Dr. Martin Makary at Johns Hopkins, they looked at all of data --

MR. MICHAEL KAWCZYNSKI: Time.

DR. PAUL ALEXANDER: Hello?

MR. MICHAEL KAWCZYNSKI: You're out of time, sir.

DR. PAUL ALEXANDER: Okay, thank you.

MR. MICHAEL KAWCZYNSKI: You can wrap it up.

DR. PAUL ALEXANDER: Yes. We looked at the children in American that have died, and we found that,

save one, most, these children had at least one severe illness. So the reality is COVID is not a life-ending, life-threatening situation for children. Right now the CDC and the NIH have not prosecuted the case as to why these children should be vaccinated. Period. I say do not do this and I beg your consideration. Thank you.

DR. PRABHAKARA ATREYA: Thank you. At this time we will conclude the Open Public Hearing and then I will hand over the meeting to Dr. Monto, the chair. Dr. Monto, take it away. I think we are getting to a break now. Would you announce the return time, please?

DR. ARNOLD MONTO: I think we now have a ten-minute break, so our busy workers who've been handling the Open Public Hearing have a little break for themselves. And we will reconvene ten minutes from now.

[BREAK]

Q&A Regarding Sponsor and FDA Presentations

MR. MICHAEL KAWCZYNSKI: Everybody else stay muted please or make sure you're muted. All right, welcome back to our 167th meeting of the Vaccines and Related Biological Products Advisory Committee Meeting. Dr. Monto, let's take it away for our afternoon portion.

DR. ARNOLD MONTO: Thank you very much, Mike. This is going to be an open Q&A session involving all the speakers we had present already. When you raise your hand and ask a question, please specify who you would like to ask the question of so we don't have a total free for all. Dr. Gruber has indicated that she does have a question she wants to raise. So I'll start with her.

DR. MARION GRUBER: Yeah, hi. This is Marion Gruber. I turn it over to Dr. Phil Krause for the question.

DR. PHILLIP KRAUSE: Yes, hi. This is actually a question for Pfizer. And of course, one of the issues in this is that much of the data that's been presented and is being discussed today is not peer

reviewed and has not been reviewed by FDA. And this includes the study from Kaiser that was presented by Dr. Bill Gruber. And so what I'm hoping is to ask a question about that study so that we can better understand some of the conclusions that come from it.

And so, what I've done here is I've taken this slide, which is being presented, Appendix 5 or Appendix Table 5, and this is the appendix from that study, from the pre-print of that study, which shows the main data in the study. And what you can see here is in 5A to left you have unvaccinated people, and to the right you have fully vaccinated people. And just to make this easy I'm focusing on people greater than or equal to 65 years of age. And you can see among the unvaccinated there were 17,278 cases and 168,143 person years.

Which then, if you do the math, you can see down here is about 1/10th of the case per person year or .103 cases per person year. If you look to the right here, the far right, if you look at the fully vaccinated people you have 594 cases among 86,806 person years. And here, that's a rate of .0068 cases

per person year. If you take these numbers and put them together you get an efficacy of 93.3 percent in the study overall in people who are greater or equal to 65 years of age.

But of course, when these studies are done, they involve fairly complicated models. And in this case, it's a Cox model which incorporates a lot of inputs. And one of the questions always, as explained by Dr. Stern, is that you have to make sure that the model is actually giving you the correct results. Because these models are complex. So my question for Dr. Gruber and Pfizer is, in a situation where the total cases tell us that the vaccine had 93.3 percent efficacy according to the data in this table, why is it this model is telling us that the efficacy is either 58 percent or 61 percent?

DR. ARNOLD MONTO: Okay, Dr. Bill Gruber. We've got two Gruber's there.

DR. PHILLIP KRAUSE: Can't hear.

MR. MICHAEL KAWCZYNSKI: Make sure you're unmuted, sir. I'll unmute you. Here we go. There you

go.

DR. WILLIAM GRUBER: There we go. Yeah, thank you. I actually joined with Donna Boyce in the same room because we had a little technical issue here. I think is a question to be best referred to Luis Jodar and his associate since they've been in close communication with Kaiser on their study. So, Luis.

MR. MICHAEL KAWCZYNSKI: Hold on a second. Dr. Gruber?

DR. WILLIAM GRUBER: Yes?

MR. MICHAEL KAWCZYNSKI: Dr. Gruber, hold on one second. I see you have -- you have multiple feeds going on over there. So I want to be sure we have clear audio for you. So let's just clean up your audio, please.

DR. ARNOLD MONTO: And I don't think it's Dr. Bill Gruber who's gonna answer right now.

DR. WILLIAM GRUBER: That's correct. That's what I was just saying. Can you hear me now or should I hold or -- tell me when I should speak.

MR. MICHAEL KAWCZYNSKI: We can hear you but

it's a lot of background noise. But go ahead.

DR. WILLIAM GRUBER: I was gonna say I think this is a question for Dr. Luis Jodar and his associate since they have been closely in communication with Kaiser Permanente about their data. So, Dr. Jodar?

DR. LUIS JODAR: So thanks for the question and the detailed analysis of the supplemental paper. As was pointed out in Dr. Stern's presentation, the critical analysis is taking into account calendar time and included in the Cox models. So this was something that, after you adjust for calendar time in the Cox models, you get a different result than you would if you didn't adjust for that.

So it is critical to include that because clearly there's a relationship between disease traits as time progresses in the pandemic and vaccine uptake. So those results that you're looking at, while they're based on accrued data, data don't account for underlying calendar time which is the critical element to include in the analysis and was included in the result that you saw in the paper.

DR PHILLIP KRAUSE: But of course, if you have this huge difference in the raw numbers and this accounting for calendar time how can you be sure that you've accounted properly for calendar time? Let's look here, for instance, under second dose partially vaccinated less than seven days after the second dose, also in people over 65 years of age where you're reporting, according to the model, 64 percent efficacy. This is before the second dose really could have had any effect. But then after the second dose you're reporting 58 percent to 61 percent efficacy.

So according to your model it looks like people actually got worse after the second dose or that the second dose really didn't do anything. Is that really what you're saying? So part of this of course is the difficulty of looking at this kind of data without having the chance for FDA to review it or allowing for peer -- this kind of data to go through the peer review process.

And what you heard of course is how much, in Dr. Gruber's presentation, Dr. Bill Gruber's

presentation, how much Pfizer is actually relying on the data from the study, which as I understand it they also co-sponsored, in reaching some of the conclusions in their study. And so, I guess maybe there are some answers to these questions. But I still do not understand how it's possible that you can have a study in which the total efficacy is 93.3 percent and you are somehow then accounting for time in coming up with an efficacy of between 58 percent and 61 percent.

Because there's nothing about this that says we're accounting for time. This is just the total efficacy over this period of time over from December 14th to August 8th. So again, this just points out the complexity of these models and the importance of these data being carefully reviewed. And I will stop there.

DR. ARNOLD MONTO: Okay.

UNIDENTIFIED FEMALE SPEAKER: Dr. McLaughlin (phonetic), could you respond to that?

DR. MCLAUGHLIN: Yeah, absolutely. So I think it's critical to include calendar time in these models. And this is a very standard way to do a Cox Model

(inaudible). So we appreciate the complexity of these models. The other thing that's important to note is that these models --

MR. MICHAEL KAWCZYNSKI: All right. Hold on a second, hold on a second. Okay, so here's what we have to do. So first off, and I want to make sure everybody can hear this because we have -- using studios and stuff like that. So number one, I need to make sure if you are not speaking, you need to be muted. And to make sure if you are listening in, do not have any audio through your own personal computers, it is all through your phone. So that's number one.

Also, at the studio over at Pfizer, please make sure all other mics are muted when you have another mic open. That'll help out a lot. All right, take it away Pfizer. Let's hope that fixes that.

DR. MCLAUGHLIN: Okay. Just a quick response. (inaudible) this is a very standard way of doing Cox Models and doing (inaudible) Cox models where you're evaluating VE in real time during a vaccine roll-out. So it's a very complex --

MR. MICHAEL KAWCZYNSKI: Okay. Pfizer, I apologize. Pfizer, you have -- again, you have multiple -- you're in a room multiple times but you have three mics that are picking up audio at the same time. So we're seeing it on our end. So I just want to make sure people can hear you. So let's just take a quick second here. We're gonna take a quick unexpected break. Go ahead and kill our feed for a moment. I'll tell you when we are clear.

DR. ARNOLD MONTO: Mike, we're gonna have to --

MR. MICHAEL KAWCZYNSKI: Okay.

DR. ARNOLD MONTO: We're gonna have to --

MR. MICHAEL KAWCZYNSKI: Yeah. But we gotta fix this. We can't hear anything.

DR. MONTO: -- move on.

MR. MICHAEL KAWCZYNSKI: I know but we can't hear anything, Arnold. So I'm gonna do a quick -- so Pfizer, I'm gonna give you about 30 seconds here. We gotta get your audio straightened out. So go ahead and let's check your audio.

DR. WILLIAM GRUBER: Yeah, one option here is we might be pulling everybody into the same room since this room seems to be working. Is that gonna work for you?

MR. MICHAEL KAWCZYNSKI: There you go. Now that's perfect. That is perfect. So put people there, tell the other ones --

DR. WILLIAM GRUBER: Yeah.

MR. MICHAEL KAWCZYNSKI: Thank you.

DR. WILLIAM GRUBER: Yeah, okay.

MR. MICHAEL KAWCZYNSKI: All right. So I'm gonna have to bring -- I'm gonna start the meeting back up. All right.

DR. WILLIAM GRUBER: All right. Thank you.

MR. MICHAEL KAWCZYNSKI: All right. Sorry about that everybody. So we're gonna go live here in a second. All right. Thank you for that unexpected quick little technical. We just wanted to make sure everybody could hear and -- as well as our members and voting members as well. So Dr. Monto, are you there?

DR. ARNOLD MONTO: I am here.

MR. MICHAEL KAWCZYNSKI: All right. I'm gonna hand it back to you.

DR. ARNOLD MONTO: Okay. I think we can summarize that there were differences in the models. And we'll let the statisticians work this out. There are often these kinds of issues when you're working with complex models. I apologize to the voting members for cutting into their time with this discussion. I'll next call on Dr. Kurilla.

DR. KURILLA: Thank you. Thank you, Arnold. This is a question for the Pfizer team. I think it's pretty clear that based on the dosing interval between the two -- between your two primary doses that while you get a nice boost in terms of antibody response you really take a big hit in terms of durability. That's very clear from the available literature on various prime boost strategies that have been done both in animals and in humans. So I think the waning of immunity should have been anticipated.

What I'm concerned with is that while it's pretty obvious that while high risk groups for severe

COVID tend to be individuals such as the immunocompromised, the elderly, obese, diabetics, all of those tend to have diminished or impaired cellular immune responses. Which is -- the exact basis of good cellular immune responses is what gives you the durability. So it's a little disappointing that there's been very little reporting of the cellular immune responses, and an entire focus on the neutralizing antisera, which clearly for that population at high risk is absolutely essential.

But for the broad population, in terms of their protection which seems to be holding up well over time, should be because of adequate cellular immune responses. But we have no indication of that. So it's unclear that everyone needs to be boosted other than a subset of the population that clearly would be at high risk for serious disease. So I'm curious as to what evidence you have in terms of cellular immune responses and how does that look in terms of durability for the average person who's been vaccinated?

UNIDENTIFIED FEMALE SPEAKER: Thank you for

the question. I will ask Dr. Gruber to comment on the cellular immunity. And then I'll also ask Dr. Phil Dormitzer to comment. So first over to Bill.

DR. WILLIAM GRUBER: Yeah. So thanks Dr. Kurilla for the question. I think we have to sort of deal with two aspects. One is the practical aspect about why we're here today. And that is of course that we're looking to try to improve on protection that is waning over time. And obviously the marker that we've used to look at that is neutralization response. Which has been a good marker albeit there are other things that accompany that type of immune response that are likely important. And so, I think, again, our goal here is to prove that the vaccine was safe and effective. Which I believe we've done.

And we've obviously met the noninferiority criteria. And I think there's every reason to believe, given the protection seen after the first dose with the neutralizing antibody and whatever came along with it, that there should be an expectation after the third dose that we continue to augment those responses. Or

at least they're no worse than they were after the second dose. And I -- you're beginning to see of course evidence of that from the Israeli study.

So I agree that it's important to understand cell mediated immune response, but I think the key message is we know protection wanes, we know a vaccine dose seems to -- based on the Israeli experience -- seems to restore that protection. We know from our own data that we're getting three-fold higher GMTs that likely are associated with good protection. But let me turn this to Phil just to comment on the nature of CMI.

DR. DORMITZER: Sure. Well, we have data on the cellular response after the initial doses where we see strong -- where we see (audio skip) seropositive T-cell responses that are as high or even a bit higher in some cases that are seen after natural infection and that in previous (audio skip)studies demonstrate that. On the sample for (audio skip) timeline, we do not yet have those data. I will reinforce what Dr. Gruber said.

That ultimately, regardless of the (audio

skip) of protection, the degree of the antibody cellular responses, it is in the end protection that matters. So ultimately the questions of mechanism are interesting but it is of course the actual efficacy or effectiveness that we observe that is the key outcome.

DR. MICHAEL KURILLA: Thank you.

DR. WILLIAM GRUBER: I think Dr. Jansen may have wanted to add a comment. I don't know, Dr. Jansen, if you're connected but we're free.

DR. KATHRIN JANSEN: Yep, I'm here. Can you hear me?

DR. WILLIAM GRUBER: Yes, I can.

DR. KATHRIN JANSEN: I'd like to --

DR. WILLIAM GRUBER: Thank you.

DR. KATHRIN JANSEN: Yeah, thanks. I'd like to make two comments. Number one, to answer the question a little bit more directly, that was just asked. We have also very good evidence of memory B and T cell responses. Which one would assume that if one gets a booster will again not be diminished but if anything sustained or go up. That's number one. And

secondly, I think T-cell responses are really not important when we look at infection. It is clear that neutralizing antibodies are responsible to prevent the infection. And what we have seen repeatedly, that we see an increase in infection over time.

We also see an increase in disease over time. Infection usually is an earlier indicator before we actually see the disease. What's important to prevent disease is both, I would think, the neutralizing antibodies as well as T-cells. But as I mentioned earlier, we have very, very strong, and this is published, B and T cell memory responses after immunization with BNT162b2. Thank you.

DR. ARNOLD MONTO: Okay. Let's move on please. Dr. Meissner. You're muted. Still muted.

MR. MICHAEL KAWCZYNSKI: Try now, Cody. Dr. Meissner. Dr. Meissner, you have your own person phone muted. Go ahead and look at your personal phone.

DR. CODY MEISSNER: Hello?

MR. MICHAEL KAWCZYNSKI: There you go.

DR. CODY MEISSNER: Can you hear me?

DR. ARNOLD MONTO: Barely.

MR. MICHAEL KAWCZYNSKI: Yes, we can.

DR. CODY MEISSNER: Okay. My apologies. And thank you, Dr. Monto. And thanks, Mike, for helping me out here. I would like to echo the comments that Dr. Monto gave this morning acknowledging Dr. Marion Gruber's remarkable leadership and contributions to CBER. And that also applies to Dr. Phil Krause. The question that I have is, what we've learned from influenza, where there's variation in the neuraminidase and hemagglutinin antigens on an annual basis we change the vaccine.

And so for a booster strain shouldn't we try and match the circulating variant as much as we can? That is, right now predominantly the Delta strain. So why did you decide, why did Pfizer decide to select BNT162b2? And this is a question for Dr. Bill Gruber. Because a new variant, when and if it emerges, will almost certainly be a progeny of the Delta variant. And don't we want to match the new strains that are most likely to circulate as closely as possible? Thank

you.

DR. WILLIAM GRUBER: Yeah. So thanks, Dr. Meissner, for your question. I think as you realize, within the flu field, flu's very different, right? We actually have major antigenic changes which we can show immunologically escape response. If someone can bring up the slide that I showed during the presentation that shows the immune response across the various variants. We see something very different here both in terms of the immune response as well as what we have experienced in terms of protection against the variant. And -- okay, there we go. If we can bring up the slide one, please, on the screen? So again --

DR. CODY MEISSNER: I remember that slide.

DR. WILLIAM GRUBER: Yeah, so this --

DR. CODY MEISSNER: But I --

DR. WILLIAM GRUBER: -- is, yeah --

DR. CODY MEISSNER: If it's going to -- sorry, go ahead.

DR. WILLIAM GRUBER: Yeah. So, I was going to say that this slide shows that (audio skip) for

variants that have (audio skip) and we also are, you know, (audio skip) looking promising for you as well. We've not yet seen a variant with this (audio skip) solution and particular circumstance of the Beta (audio skip) spike variant (audio skip) at least have (audio skip) a neutralizing titer of (audio skip).

So at the lowest of the group we had a 0/9 lift, in South Africa (audio skip) in terms of protection against that particular variant. So that does not mean perhaps some time in future there may be a variant that (audio skip). Right now there is not one. We are obviously (audio skip) as the variant expresses (audio skip) there seems to be potential for a (audio skip) very interested in pivoting very quickly to bring that variant on board.

But at this point that does not seem necessary and I (audio skip) from what we've seen in Israel (audio skip) Delta, which (audio skip) because you've restored, when to receive the booster, at 95 percent. You know, we have looked, as I mentioned, at Beta as a surrogate so that would be able to pivot, potentially,

in the future without having to do additional clinical trials so we could rapidly react.

But for now, there is no evidence of escape for the variants we've looked at. The efficacy data from South Africa suggests even when it's a little bit lower we're protected. And the information from Israel shows 95 percent restoration of protection after a booster. So I think the flu story is different.

DR. CODY MEISSNER: But I think there are certain similarities, Bill, in the sense -- in your trial I know that six patients, six subjects of the 312 received a prototypic Beta vaccine. And my point still arises, the new variants that are very likely to emerge will most likely come from the Delta strain. And they will have either increased capacity for transmission and hopefully not increased capacity for disease, but it's hard to predict at this stage. And don't you want to introduce a new vaccine that's going to be most similar to the ones that are likely to emerge in the future?

DR. ARNOLD MONTO: Cody?

DR. CODY MEISSNER: Yeah?

DR. ARNOLD MONTO: I'm gonna park the answer to that question. We all know what the answer would -- we would like to see. But we've got a question in front of us right now. So please, let's move on. I just want to remind the committee that the people in -- our colleagues in Israel are staying up late to answer our questions. And if there are questions for them I would like to give that priority. So I can't see because there's a share my screen in front of the -- okay, now I can see. Dr. Hildreth. Muted.

DR. JAMES HILDRETH: Pardon?

DR. ARNOLD MONTO: Okay, we hear you.

DR. JAMES HILDRETH: Thank you, Dr. Monto. Can you hear me now?

DR. ARNOLD MONTO: Yes.

DR. JAMES HILDRETH: Okay. My question is for the team from Pfizer or from Israel, for that matter. It is not unexpected that the antibody levels would wane after the vaccinations. But has anyone attempted to correlate a certain titer with protection? Because

if we knew the minimum titer needed for protection that would be a great way for us to monitor whether or not we really needed booster shots. So is that anything someone on the team can speak to, please?

DR. ARNOLD MONTO: Anybody from Israel want to talk to the data from Sheba Medical Center?

DR. JAMES HILDRETH: I can't hear her, Dr. Monto.

DR. ARNOLD MONTO: I can't either.

DR. SHARON ALROY-PREIS: Yeah, I have to unmute first.

DR. JAMES HILDRETH: Okay, thank you.

DR. SHARON ALROY-PREIS: Yes. We're doing research with Sheba Medical Center that involves families of confirmed cases. So we have taken confirmed cases and registered their family members who were vaccinated into this research that follows them for 10 days. And then try to establish whether they were confirmed on the first PCR being enrolled into the study and then on day 10. And at the same time, upon enrollment, we're taking antibodies, neutralizing

antibodies and cell mediated immunity levels to try to find out the correlation of protection. Hopefully, we'll have that result in a month.

DR. JAMES HILDRETH: Okay. Well, that would be very helpful to have.

DR. ARNOLD MONTO: The bottom line is we do not have a correlative now which is --

DR. SHARON ALROY-PREIS: No.

DR. ARNOLD MONTO: -- part of -- part of the -- okay.

DR. JAMES HILDRETH: Thank you.

DR. WILLIAM GRUBER: Dr. Monto?

DR. ARNOLD MONTO: Yes?

DR. WILLIAM GRUBER: I'm sorry to interrupt. Would the -- is it permitted for Dr. Jansen -- she'd like to just comment on that last point if it's okay?

DR. ARNOLD MONTO: Okay, yes. Quickly please and without a -- and I hope we can hear her. It's a chronic problem from your --

DR. WILLIAM GRUBER: She's in an -- yeah. She's in Berlin and seems to have a better connection

all the way from there than we do. So hopefully so. Go ahead.

DR. KATHRIN JANSEN: German technology. I'm just kidding. I just wanted to say that we actually looked in our breakthrough cases in our placebo-controlled phase III study and have compared the antibody titers where we had the opportunity in individuals who got the disease versus the ones that didn't. And we were also unable to really come up with an antibody threshold. So I think it's probably a much more complex story and not just easily addressed with neutralizing antibodies. Thank you.

DR. JAMES HILDRETH: Thank you.

DR. ARNOLD MONTO: That sounds reasonable. Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Yes. Thank you, Dr. Monto. My question actually is for Dr. Oliver if she's still here. Or anyone on the epidemiology side. So it appears that what's happening with regard to breakthrough infections among the vaccinated is different in the U.S. compared to what's happening in

Israel. The DELTA variant has been, I think, prominent during the same period of time in both countries. And yet the outcomes seem to be quite different. Can you shed some light on that, Dr. Oliver?

DR. SARA OLIVER: Yes. Hi, thanks. So I don't know that I will have kind of the definitive answer. I can give a couple of thoughts. First of all, I would note that the definition of severe disease that Israel has used is quite different than what we've used in the U.S. So they have said that an elevated respiratory rate or an oxygen level less than 94 percent is severe disease. Whereas CDC, in the studies, has primarily been, you know, clinical hospitalization, ICU, or death. So that is one aspect when we try to compare point estimates.

I think another thing that is likely important is just the size of the country and the heterogeneity of the pandemic across the U.S. When we look and combine data, you know, across 50 states, these broad platforms, that it's likely just very heterogenous compared to a smaller country. As well as the way the

vaccine has rolled out. That they achieved high vaccine coverage very quickly. Whereas, you know, in the U.S. we've had a little bit more of a rolling kind of gradual uptick.

So, you know, I think there's a variety of factors that could play into it but those are the first three that come to mind. And we, I will also say -- they kind of exclusively have used Pfizer. We have a variety. We've used Pfizer, Moderna, and J&J. And so it could be that the heterogeneity of vaccines used as well could be a -- somewhat of a role in what the U.S. is seeing.

DR. ARCHANA CHATTERJEE: Thank you. I think it's important to note that the difference is quite striking. Because from CDC data that we're all looking at it appears that only 2 percent of the hospitalizations, if you're just looking at hospitalization data, are among vaccinated individuals in the U.S.; has been true for many weeks now. Whereas that is not true, according to the data that was shared with us from Israel, which seem to be only 40 percent

of their hospitalizations were among those who were unvaccinated. So I'd just like to point that out to the committee. Thank you.

DR. ARNOLD MONTO: I think there's a difference in the percent in the country that are vaccinated. Which is -- which may be a factor there. Dr. Pearlman.

DR. STANLEY PERLMAN: If I may --

DR. RON MILO: Actually, Dr. Monto?

DR. ARNOLD MONTO: Okay, Dr. Milo?

DR. RON MILO: If I may just add one sentence. I think the proportion in Israel -- as Sharon presented, most of the elderly population in Israel had been vaccinated very early, almost all around the month of January and February. And I think that is also a difference that most of the population now are about six or seven months post their vaccination.

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

DR. STANLEY PERLMAN: Yes. So I want to ask a question. It's a continuation actually of these questions. So in Israel there's both the question of

the high vaccination rate that was just pointed out and also the fact that in the last one or two months there's been huge gatherings within Israel whether over the high holidays or other venues. And when you do your analyses and try to compare the effects of vaccination on boosting, certainly the data show that boosting is very effective.

But when you put these other factors in how strong are the data, if you subtract these other issues, how strong are the data supporting, really, a booster immunization?

DR. RON MILO: Okay, so maybe I'll begin and maybe Dr. Preis will continue. So the analysis that we did was either in the month of July or in the month of August. Those gatherings you referred to on the high holidays, we really are in that season now during September. So all of those studies that I've shown you are actually still in the month prior to the gatherings and the high holidays.

DR. WILLIAM GRUBER: Dr. Monto, this is Bill Gruber again. Could I have your indulgence to have

Luis Jodar comment on this? Obviously in part because we didn't get a change, due to my running over time, to speak to out interpretation. So Dr. Jodar?

DR. LUIS JODAR: So, Bill, thank you very --

DR. ARNOLD MONTO: Well, I wish we didn't have to hear you twice but we have feedback again.

DR. WILLIAM GRUBER: Really?

DR. LUIS JODAR: So you cannot hear me? Do you hear me with an echo?

DR. ARNOLD MONTO: With an echo.

DR. LUIS JODAR: We apologize --

DR. WILLIAM GRUBER: We don't have any --

DR. LUIS JODAR: -- for any technical --

DR. WILLIAM GRUBER: We don't have any mics.

DR. ARNOLD MONTO: Why don't we move on and then when we get a chance we'll go back to you. Because it's a real problem. Amanda Cohn, Dr. Cohn.

DR. AMANDA COHN: Thank you. Can you hear me?

DR. ARNOLD MONTO: Yes, perfectly.

DR. AMANDA COHN: Great. I have a question specifically for our colleagues in Israel. And it's

two parts. One is whether or not in the breakthrough cases that you have seen, but in particular in young adults, if you've seen reports of myocarditis, long COVID, or MISC in those young adults who had two doses but had breakthrough disease? Or were most of those cases asymptomatic or mildly symptomatic with no long-term sequelae? And then second, can you explain -- I think we got to part of this answer in the last question.

But why is it that if your r-knot (phonetic) went below one, in recent weeks you started to actually -- you're at your highest rates right now and your test positivity rate is increasing at least from the data that you have online from the last couple of weeks?

DR. SHARON ALROY-PREIS: I'll start with the second question. And that goes to the high holidays and this very weird period. And in addition, the first of September when we opened schools despite the increase of the fourth wave. So I think the combination of these things in September are making our numbers a bit funny and not really reliable. But we do

know, we are aware of the fact that we are in the fourth wave. We are not at all in the end of it. We are still with high numbers with 6 percent to 7 percent positivity in test results.

And I think once the holidays settle down, we'll see the true effect of where we are. But until the high holidays, we saw, as Ron showed, a continuous drop in the reproductive number and in stabilization in the active severe and critically ill patients. So we definitely feel the booster effect but we're not over the fourth wave yet. And you need to remind me the first question. Sorry.

DR. AMANDA COHN: Sorry, thanks. It was just related to, in younger adults who had two doses have you had any reports of -- in breakthrough cases of myocarditis or long COVID or MISC?

DR. SHARON ALROY-PREIS: We had cases of myocarditis and long COVID in young adults, as I've shown you before. It was mainly with males in their thirties. And that was the signal -- the very clear signal was after the four, in the four or fifth day

after the second dose. So there was like an epidemic curve after the second dose. Nine-five percent of them were not severe, were discharged after a few days in the hospital. And we have seen, in this fourth wave, hospitalizations of people who are younger than 60 years old.

Some of them with mortality who were doubly vaccinated and did not receive yet the third dose. So among the mortality, one of the speakers in the public hearing actually referred to us having a high rate of mortality in Israel, about 1,000 people dying in this fourth wave. And that is true. But 40 percent of them are unvaccinated and 54 percent of them received two doses and did not have the chance to receive the third dose yet. And the minority are those who were in between vaccinations or in the process of being vaccinated.

And a real minority received a third dose and died from Corona. So it is clear that in our fourth wave the vaccinated, doubly vaccinated individuals, play a major role. Not just in confirmed cases but

also in hospitalized, in severely ill, and critical ill and in death. I hope that answered the question.

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

DR. HAYLEY GANS: Hi. Thank you so much. I did have a follow-up to -- for our Israeli colleagues. Because I had brought up the idea of secondary cases (audio skip) but the real part of that question that I thought was of interest today is -- and maybe you can't say this because September has been an odd behavioral month. I'm wondering if actually the third dose has brought those secondary cases down in people who are immunized (audio skip) spread. Again, I was just saying (audio skip) to younger individuals. That would be a real reason (audio skip) stop the spread. I was wondering if you could speak to that dynamic (audio skip) that we are experiencing here in this country?

DR. SHARON ALROY-PREIS: So I have to say that for the first time I was able to unmute my phone and then talk. All the previous times I talked first and then unmuted. So yes, we have seen a decrease in the

number of people who are getting infected from people who are now with a booster dose. It's not -- we haven't done yet the full analysis of that. We're in the midst of that. But I think that the fact that the reproductive number is coming down, this is what it means.

Every one person who is confirmed actually infects less people. So that is clearly part of the equation now. The people who are thirdly vaccinated, doubly vaccinated with a booster are getting less infected and are less infecting others once they're confirm. But this is real preliminary result.

DR. HAYLEY GANS: Thank you. And the only safety question I had, that probably pertains to our U.S. data. And hopefully those who are ongoing studying this (audio skip) in the other safety nets that continue. There's already been about 1 million third doses that have happened in the U.S. and I'm wondering if somebody from the CDC can talk about the safety.

DR. SARA OLIVER: Hey. Yes, I would say stay

tuned. I think there's a upcoming analysis on this that could come out within the next week or so. So I don't have the data right in front of me but I know that that is actively being investigated and will be reported very soon.

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

DR. MARK SAWYER: Thank you very much. My question is for Dr. Lee or colleagues at FDA. And it sort of extends Dr. Gans line of thinking just now. And it's about the safety profile. As I understand, clearly the mRNA vaccines are among the most reactogenic of any vaccine we've given in recent years. As I understand the question posed for the committee today, we are not to consider the data from Israel. We're supposed to look at the sponsor's data from their clinical trial.

And I came into today thinking that was a very small safety database of 300 people. So I'm interested in comparison to other vaccines that we have decided to give a booster dose for in recent years like meningococcal conjugate vaccine, meninge B vaccine,

Tdap, what is the size of the database in those studies? I took from Dr. Lee's presentation that FDA is comfortable with this sample sizes of 300. But it strikes me as a little bit small.

DR. DORAN FINK: Hi. This is Doran Fink. Can you hear me?

DR. ARNOLD MONTO: Yes.

DR. DORAN FINK: Okay, thanks. So the size of the safety database that the FDA has relied upon to support licensure of booster doses for preventive vaccines has varied somewhat. It depends in large part on the understanding of the safety profile from the primary series both in terms of clinical trial data, some pre-licensure studies, as well as post-licensure safety experience. So, for example, in the case of the Japanese encephalitis vaccine, IXIARO, we had a booster dose clinical trial safety database of about 300 adults, mainly younger adults.

But also, some post-licensure safety experience, although not huge. In the case of several meningococcal conjugate vaccines the pre-licensure

safety data for booster doses has been somewhat larger than that, nearing 1,000. And with perhaps more post-marketing, post-licensure safety experience there a well. And then with tetanus, diphtheria, and acellular pertussis vaccine approved for a second dose in adults, again, we have the clinical trial safety database preceding licensure of a booster dose of about 1,000 or so, and extensive experience with that vaccine being used off label as a booster dose.

In the case of these COVID vaccines, yes, these pre-licensure clinical trial database is around 300 which is on the lower end of the range that I just mentioned. But we also have a very extensive post-authorization safety database for the primary series that we can consider as well. Does that answer --

DR. MARK SAWYER: Thank --

DR. DORAN FINK: -- your question?

DR. MARK SAWYER: Yes. Thank you, very much.

DR. ARNOLD MONTO: Thank you. Dr. Portnoy. And one more question after that before we move on.

DR. JAY PORTNOY: Okay, thank you. So I guess

my question is for the Israeli group. Because our job is really to determine the risk versus the benefit of the COVID vaccine, a third dose, versus just going with two doses. The emphasis in Israel was on reducing the rate of infection using the third dose because infection rates were starting to go up. We know that people who get the COVID infection also have the side effects. They get myocarditis, they have adverse events and so on. And we're trying to compare the rate of those with the rate of getting the same adverse events from the vaccine.

I was just wondering, in the Israeli experience, when the number of people who had the two vaccines but not the third one, did they see a decrease in the frequency of getting the infection after the third dose? Was the decrease enough to also reduce the rate of getting these adverse events from the actual infection as opposed to getting the same effects from the vaccine? Did you compare the two?

DR. SHARON ALROY-PREIS: I'll try to answer. So I think the third dose reduces your risk to get an

infection. So it reduces significantly a risk of getting adverse events or reaction or complications from the disease itself. Because you are more protected now. And you're getting vaccinated basically to what we saw after the second dose, pre-waning effect. I have to say that I was pretty surprised with Retsef Levi's comment that Israel doesn't follow adverse events. It's our data, I'm in charge of it, so I know exactly what is being reported to us.

And I set our reservation. But we actually have two very large studies from our biggest HMOs that covered 75 percent of the population. And they looked into adverse events in Maccabi and Clalit. They looked at adverse events one week following the third dose in those who are 60 plus. And they saw the same thing we saw, that there was the same -- there was some local and systemic adverse events but not serious adverse events.

Most people said that they felt like they felt after the second dose, between 80 percent to 90 percent said they felt like after the second dose, and about 10

percent said that they felt worse but there was no adverse event. And about 1 percent went to seek medical help because they didn't feel well. So it's really not significantly different than what we saw on the second dose. So the adverse event from the third booster dose, based on our 3 million vaccinees -- and I have to say again, part of them have not -- we haven't followed for 30 days.

Because we just rolled for the younger adults recently. But for the older people we have passed 30 days and this is the profile that we're seeing. Pretty safe. And we saw an increase in -- dramatic increase in their protection against disease. So the risk of them having disease with complication reduce significantly.

DR. ARNOLD MONTO: Thank you.

DR. JAY PORTNOY: So adverse events might have been less than the risk of getting those same events if they were not vaccinated and they just got the disease.

DR. SHARON ALROY-PREIS: So what we saw prior to our booster campaign was that the 60 percent of the

people in severe and critical conditions were immunized, doubly immunized, fully vaccinated. And as I said,45 percent of people who died in this fourth wave were doubly vaccinated. So there was a huge importance of this booster effect not to just to reduce confirmed cases but actually to save lives for those who are getting the disease and those who are getting the severe and critical conditions.

DR. JAY PORTNOY: Thank you.

DR. ARNOLD MONTO: Thank you. We're moving on to Dr. Levi.

DR. Ofer LEVI: Can you hear me?

DR. ARNOLD MONTO: Dr. Levi?

MR. MICHAEL KAWCZYNSKI: Yes, we can hear you, Dr. Levi.

DR. Ofer LEVI: Great. Well, I wanted to thank Dr. (audio skip), particularly on the Sabbath. Shabbat Shalom. I know you (audio skip) in your prior answer. But I specifically wanted to drill down to males where that group appears to suffer the highest risk of vaccine associated myocarditis. And

specifically around the booster doses do you have data, do you have numbers to say whether the risk -- I'm particularly thinking 16, 17, 18 years of age, whether that number is similar to that after the second dose?

How does that compare with the third dose specifically in that group? Thank you and Shabbat Shalom.

DR. SHARON ALROY-PREIS: Thank you for the question. So you could pull up the slide. I think one before the last from my presentation. But basically, what we did in the first and second doses back then when we had a signal of myocarditis -- and we actually heard it from, you know, from people in the hospital that they are seeing epidemiological analysis of that by three different groups, trying to figure out if this is a true signal. And the article is about to be published on that topic.

And we did see a signal after the second dose, as I said, with a rate of about -- the highest rate was about 1,000 to 6,000 vaccinees among 16 years and up, to 10,000 in the older group, age group, between 20 and

29, and over that when you go up by the age. We have vaccinated more than 6,000 people at the age we are talking about and we haven't seen the same adverse event. And I want to emphasize again that for myocarditis we are actually doing active surveillance.

We are calling the hospital every week to find out about new cases, regardless of vaccination. They are supposed to report to us all case of myocarditis. And so we are really on top of the myocarditis issue. The only report that we had so far was of one case, 30 years of age, that I showed. But I want to be very, very clear that we have not followed them yet for 30 days. So we'll continue obviously to follow.

But the results that we have so far from the active surveillance are reassuring to say that at least for now we have a lower rate of myocarditis than we saw on the second dose.

DR. ARNOLD MONTO: Thank you very much. And I think we can excuse our speakers now because we're in transition to our next session which will be led off Dr. Peter Marks.

UNIDENTIFIED FEMALE SPEAKER: Sorry, Dr. Monto, would it be possible to have one more comment from Pfizer? I think we finally have a phone line that works.

DR. ARNOLD MONTO: Oh, okay.

UNIDENTIFIED FEMALE SPEAKER: Sorry.

DR. ARNOLD MONTO: Let's have Pfizer give us their last comment which I cut off.

DR. LUIS JODAR: Sorry, Dr. Monto. This is Luis Jodar. I am the chief medical officer for Pfizer. I just wanted to give perhaps a little bit, a different interpretation. I do not necessarily think that the epidemiological patterns that you are seeing in Israel are significantly different to what you're seeing in the United States or elsewhere. I mean, I actually think that Israel saw it first because as Sharon Alroy-Preis said they were just three months ahead. And if you look at the epidemiological patterns, and I'm not discussing about the Kaiser Permanente.

I'm discussing about the CDC, I'm discussing about the Public Health England, discussing about

Qatar. You'll see the epidemiological pattern of reduction in all the other countries starting with infection. And it's not only infection, I would just say it's infection and symptomatic disease, going down to 60 percent 50 percent in all these countries. And again, if you look at the MMWR reported today here in the United States you start to see even hospitalization going down 77 percent.

So the conclusion is that the epidemiological patterns around the world are remarkably similar to what we have seen in Israel so far. It's just that Israel, again, has said before they just vaccinated many more people much earlier. So I just want to make that position. Thanks.

DR. ARNOLD MONTO: Thank you. And now to Dr. Marks. You're muted.

DR. PETER MARKS: Hi. Sorry, double muted there. Sorry, my apologies. Thanks very much, Dr. Monto. I just want to take this opportunity to again thank the committee members and chair and our invited speakers and the FDA staff from the Office of Vaccines

along with the advisory committee meeting staff who have made this meeting possible. I also want to take this opportunity to deeply thank doctors Gruber and Krauss for their incredible work in the past decades in the service of public health and particularly during the century's worst pandemic.

As I noted this morning, the decision the FDA needs to make is based upon complex data that's evolving in front of our eyes. There are different views of the data and discussion of differing opinions is critical to assist us in making our regulatory determination. It's no secret here that there is still debate over the need for an additional COVID-19 vaccine at this phase of the pandemic. But the emerging evidence such as that from our Israeli colleagues is very helpful.

We also know that breakthrough infections, including some that are severe, are occurring in the United States and FDA is tasked with reviewing an application that shows data highlighting the need and potential benefit of a third dose for the prevention of

COVID-19 due to SARS-Coronavirus-2. And in this regard, I want to bring two points to the attention of the public and to the committee. And if I could have the slide? Okay, let's see if we can get the slide that I asked for up. While they're doing that I'll just go ahead.

First, the need for an additional vaccine dose at six months should not be surprising based on our knowledge of the immune system and our experience with other vaccines. I think this was already referred to by Dr. Kurilla. As shown here on the CDC's ACIP adult immunization schedule for 2021 nearly half of the non-influenza, non-live virus vaccines require a second and third dose, including a dose at six months. Therefore, the need for an additional dose at six months to provide longer term protection should not come as a surprise as it's likely necessary for the generation of a mature immune response.

And acknowledging the continuation generation of evidence that we have for the COVID-19 vaccines this may end up being the case here as well. Second, the

vaccines for other diseases noted here that are given to adults are not only indicated for the prevention of severe disease or hospitalization. Realizing the benefits of reducing disease occurrence or transmission these other vaccines are indicated for various severities of disease prevention and the attendant population.

Similarly, the question of safety and effectiveness for the third dose of Comirnaty before us today may not just be related to preventing severe disease requiring hospitalization, but also to preventing cases of COVID-19 that are associated with significant morbidity, including debilitating symptoms such as long COVID. There's also the issue of preventing the continuous spread of COVID-19 to vulnerable populations, particularly children who are of an age where they cannot yet be vaccinated.

So to conclude, as you enter your deliberations. I greatly appreciate the work of the committee members helping to sort through the data and make a recommendation which is a critical step as the

agency moves to act on the application. And does its best to ensure that the rational for its decision is clear. Not only to healthcare providers but also to the American public. We look forward to your deliberations and thank you so much, all, once again for taking the time.

DR. ARNOLD MONTO: Can we introduce the voting question and have some clarification about what we are to consider in responding to the vote?

DR. PETER MARKS: I will turn this over to my FDA colleagues who will bring up the voting question.

COMMITTEE DISCUSSION AND VOTING

DR. PETER MARKS: So that question is here now. Do the safety and effectiveness data from -- go ahead, Marion. Thank you.

DR. MARION GRUBER: Yeah. Thank you. And thank you, Mike, for putting up this question. So we have one voting question: Do the safety and effectiveness data from clinical trial C4591001 support

the approval of a Comirnaty booster dose administered at least six months after completion of the final series for use in individuals 16 years of age and older?

DR. ARNOLD MONTO: The point of information I would like to ask is whether we are permitted to use any data from outside that extended clinical trial in our consideration in the vote?

DR. MARION GRUBER: Well, we do make a regulatory decision, of course, based on the safety and effectiveness data that are derived from the clinical trials with that very product. However, as I mentioned in my introductory remarks this morning, we also look at the benefit and risk of this additional booster dose when making a decision as to whether this dose is safe, and the benefit-risk consideration of course will look at the benefits. In this regard, of course, the data and the presentations that you've heard today will also be considered in making this decision.

So in other words as you're doing your vote, please look at the data derived from the clinical

trials. But if you look at benefit-risk, of course that supportive information will certainly factor in.

DR. PETER MARKS: Yeah. This is Peter Marks. I just wanted to summarize here very clearly. You are allowed to look at the totality of the evidence in order to make your recommendations for us. That is the totality of the evidence before you, just like we will. We are a science-based regulatory agency, and that means the person that ignores data is the one that's surprised. We're not going to ignore data, just as you don't have to. This is not a legal proceeding. This is a scientific proceeding, so you can take all the data into account. Thank you.

DR. ARNOLD MONTO: Thank you for that clarification. Okay. We have hands being raised now. Dr. Hildreth, is that a new hand being raised, or is that the old one?

DR. JAMES HILDRETH: Well, since it's raised, I will take this opportunity. Is that all right?

DR. ARNOLD MONTO: That's fine.

DR. JAMES HILDRETH: I have three

considerations that are important for me. One is I was hoping to hear from either Pfizer or the folks from Israel that there was a neutralizing titer that correlated with protection because that would allow us to determine whether or not antibody levels had waned enough to make boosters necessary. That'd be a very objective way to make that decision. I have a serious concern about myocarditis in young people. If it's related to the immune response and the booster shots induce a very strong response, is that going to amplify the risk for myocarditis in those individuals?

And like Dr. Meissner, I also wonder whether or not boosters would be best if they matched the variants that are causing so many challenges now. And the mRNA technology should make that reasonably easy to do, so those are my three considerations in all of this. Thank you, Dr. Monto.

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

MR. MICHAEL KAWCZYNSKI: Dr. Levy, you're unmuted. You can turn your camera on.

DR. OFER LEVY: Oh, no. Sorry, that was an

error.

MR. MICHAEL KAWCZYNSKI: All right.

DR. ARNOLD MONTO: Okay. Dr. Gans, is your hand raised again?

DR. HAYLEY GANS: Yeah. Thank you for this ability to have this conversation. I am struck by FDA asking us to look at the totality of evidence when there's several key points, I think, that we're lacking right now. One of them is the very strong safety data that we could have actually with all the third doses that have been given. We are given some support and (audio skip) from the Israeli data, but I think that that's a really missed opportunity and something that should be considered when the FDA considers. 300 people is not a large enough study, but we have other data that could be looked at.

The other thing, along with Dr. Hildreth, that I think is very important is another missed opportunity that I think the FDA could have asked for is actually looking at those pre-third dose both humoral and T cell immunity and really trying to parse out what happens in

that, plus the fact that we have a lot of breakthrough. So we really could have the answers, and to be asked that they're complicated assays or to be told it's up and coming it feels that we're making decisions when there's data out there that (audio skip). I think that it's very important what the Israeli study showed, if it truly does show that secondary infections have been reduced by the ability to (audio skip) because I think that is one of the (audio skip), so I was encouraged by that. Those are my considerations as (audio skip), but I just wanted to put that plug in.

The other piece that I would like to put in a plug for is that Pfizer should be looking at alternative schedules as well. It is true that we sometimes do prime-prime-boost, but we really haven't seen other vaccines that use three (audio skip). So there should be some consideration not only to looking at different variants but looking at different schedules.

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

DR. PAUL OFFIT: Thank you. So here's how I

put this together. I think the stated goal of this vaccine by people like Rochelle Walensky and others has been to protect against serious illness. And the data that were presented to Sara Oliver and by Kathleen Dooling previously at the ACIP meetings shows that these vaccines do exactly that. And it's exactly what you'd expect.

I mean, these studies are consistent with the fact that protection against serious illness is mediated by memory B cells, which as has been shown by researchers like John Wherry here at Penn as well as Shane Crotty at La Jolla are long lived induced by two doses of mRNA containing vaccines and have plenty of time to activate and differentiate to protect against serious illness which takes a longer period of time. It's hard for me to understand at some level the Israeli data, which are at variance with these studies. But it's especially hard for me to buy the fact that because they started, say, doing their immunization schemes three months before us that that's why they're seeing what they're seeing because all the data are --

the longevity of memory T cells is far longer than that, unless what we're arguing is that those who are greater than 60 or 65 have a lower frequency -- much lower frequency of memory B and T cells and therefore are more fragile and more quickly seen as being susceptible to severe disease.

It's also clear, however, that the third dose of mRNA vaccines increases the titer of virus specific neutralizing antibodies and will likely decrease the incidence of asymptomatic or mildly symptomatic infection, which is associated with contagiousness. So then the question becomes what will be the impact of that on the arch of the pandemic, which may not be all that much. I mean, certainly we all agree that if we really want to impact this pandemic, we need to vaccinate the unvaccinated.

And then my last point and then I'll stop is just to sort of underline Dr. Hildreth's comments that we're being asked to approve this as a three dose vaccine for people 16 years of age and older without any clear evidence of a third dose for a younger person

when compared to an elderly person is of value. If it's not of value, then the risks may outweigh the benefits, and we know that the 16 to 29 year old is at higher risk for myocarditis. And now we have an even greater booster response, and that's seen after the second dose.

So I guess in summary I would say that while I would probably support a three dose recommendation for those over 60 or 65, I really have trouble supporting this as written for anyone greater than or equal to 16. Thank you.

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

DR. MICHAEL KURILLA: Thank you, Arnold. Yeah. I need some clarification from FDA regarding their question. So is the question really getting at changing the primary vaccination to a three dose regime, or is it just for the third booster this time? Or is it for a booster every six months at this time going forward? That's one. So I'd like the FDA to comment on that.

I agree with a lot of what Dr. Offit said with

the caveat that I was a little surprised at the response by the Pfizer team that they find they have very good B and T cell immunity, and yet they're saying that they have -- they don't see good durability. So they need to have a boost. It's a little bit conflicting to me in that regard. I can understand where certain populations -- Dr. Offit mentioned the elderly -- I think also the immunocompromised.

There are some very clear populations that have impaired or diminished good cellular responses, and a boost may be very appropriate for them. It's not clear to me that the data we're seeing right now is applicable and necessary general population.

DR. ARNOLD MONTO: Dr. Marion Gruber, your answer.

DR. MARION GRUBER: Yeah. I just wanted to clarify for Mike, you know, going back to his initial question. The reason why we posed the question the way we did is because Pfizer did ask for an indication for an additional -- not an additional dose, for a booster dose -- a single booster to be administered six months

following the primary series. And I know there are different perspectives whether the third dose can be seen as part of the primary series or not. I think the perspectives are different here, but that's really beside the point right now.

What Pfizer has asked is for a single additional dose which is a booster dose administered six months after the primary series. And that is -- because that was a request from Pfizer, that's why we phrased the question whether the safety and effectiveness data would support approval of a booster dose administered six months after the primary series.

DR. MICHAEL KURILLA: But would the expectation for people who are unvaccinated at this point -- were a third booster dose to be approved, the expectation is that they would be told the primary vaccination scheme would include three doses? And how does that impact the pediatric indications?

DR. MARION GRUBER: That may be the case for the unvaccinated. Of course, they would need to get their primary series, but they would not at this point

go ahead and say a primary series requires a booster dose.

DR. MICHAEL KURILLA: Thank you.

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

DR. CODY MEISSNER: Thank you, Dr. Monto. I'd like to just give a couple of thoughts as I listened. First of all, I agree with Dr. Gans that we still don't know the proper interval between doses, and I would add to that we don't know the proper dose. And there is some preliminary data regarding another messenger RNA suggesting that a lower dose might be effective, and it might be less likely to be associated with complications.

Secondly, I think one of the arguments in favor of giving a booster dose is the data on sterilizing immunity. That is if a third dose does in fact reduce the risk of transmission, then that's a significant observation. It still sounded as though it's premature to come to that conclusion.

In terms of what Dr. Marks said, I think it's

very reasonable that for most killed vaccines indeed we do need to have an interval of time and a booster dose months after the primary series. But my concern -- and perhaps the FDA could comment on this -- Israel we just heard is experiencing myocarditis in the high risk young adult male group at about one out of 6,000. In the United States going by their recent ACIP data describing 50 to 60 cases per million second doses, it comes down to about one per 20,000. And we really don't know what's going to happen after a third dose. Myocarditis may be less common. It may have similar rates of occurrence, or it could be more common.

We understand so little about the pathogenesis that it seems to me we need to know that data before going forward with a booster dose for the general population. One of the thoughts that has come up is why can't Pfizer check component levels, for example. Might there be some clinical myocarditis that occurs after third dose? Could they look at component levels or another parameter before and after administering that third dose to give us some reassurance that we're

not causing a problem?

DR. ARNOLD MONTO: Dr. Fink, I see you. You've come on. Do you have the answer?

DR. DORAN FINK: I don't know if I have the answer, but I can offer some comments from the FDA perspective. So first of all in terms of the risk of myocarditis, pericarditis that we're seeing here in the U.S., yes, the most recent VAERS data are showing reports of myocarditis, pericarditis in a range of 60 to 70 cases per million doses in the 16 to 17 year old age group, which is the highest reporting rate among the various age groups that examine. That is numerically lower than the one in 6,000 rate that you just heard about from Israel.

On the other hand, we do know that VAERS is a passive reporting system, and when we query healthcare claims databases such as Optum as was summarized in our clinical review and summary basis for regulatory action or the original BLA from Pfizer, what we find is actually an estimate with some fairly wide confidence intervals -- but an estimate of around 200 cases per

million doses in these 16 to 17 year old age group, which if you do the math is about one in 5,000. So that actually is fairly similar to what the Israelis are finding.

As you stated, we really don't have enough data yet to know what the risk of myocarditis or pericarditis would be in any specific age group following a booster dose. It is an important question. It is likely one that can only be answered in the context of post-licensure or post-authorization use. But also we agree with you completely that it is important to study whether initially some clinical cases of myocarditis may be occurring and, if so, what the outcomes of those cases are. And we have discussed the need for such investigations with vaccine manufacturers, and perhaps Pfizer would like to explain what their plan is for investigating that possibility.

DR. ARNOLD MONTO: And to continue the discussion, is it possible to say at what age myocarditis aims to not become a problem, to put you on the spot?

DR. DORAN FINK: If you look at the healthcare claims data, you see that there is evidence of some attributable risk at all age groups, although the older you get the higher the risk for complications from COVID that then offset the risk for myocarditis. So when you look at the balances of risks versus benefits, we really start to see a risk of myocarditis being higher in males under the age of 40. And that's what is written in the warnings.

DR. ARNOLD MONTO: Thank you. Let's move on, and then we can ask Pfizer for comment later on after the list of those with their hands raised has been handled. Dr. Rubin is next.

DR. ERIC RUBIN: Thanks, Dr. Monto. I'm going to echo something that most people have said, but I want to just say it in a slightly different way. We're waging risk and benefit here, so we really have to think about both. We don't know that much about risks. The truth is a very small number of people under 60 have received the vaccine, but there is a lot of Israeli data that suggests it's probably okay in people

over 60. But we know very little about people under 60 because it's been such a short time since they started vaccinating. So that's where the risk calculation stands.

There's a big difference between the U.S. and Israel. The use case in Israel is there most kids are vaccinated. If it really does limit transmission, then it will be important to take those vaccinated people and further limit transmission in them. But remember in the U.S., transmission's going to continue to be driven by the very large number of unvaccinated people, and the marginal benefit of a third dose of vaccine for people who are already vaccinated is likely to be very small for reducing the overall burden.

So that really means that the primary benefit is going to be in reducing disease, and that's largely been defined in various ways as severe disease. And we know the people who benefit from that. They're the people who are at highest risk of severe disease, which means older people and people with other comorbid conditions, and those are the kind of people that the

FDA has already approved a third dose for, although so far it's a relatively contained group. So I suspect that many of us are heading toward the suggestion that we can find vaccination at this point to that group.

I will add I strongly suspect that when we see data, that it will prove -- and this is going to be confusing. But it will prove that there is a very low risk of the vaccine, but we don't have that right now. And I don't think that I'd be comfortable giving it to a 16 year old for all the reasons that everyone has already raised.

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

DR. OVETA FULLER: Thank you, Dr. Monto. I think what I wanted to say has essentially been addressed by Dr. Rubin in that we don't have the same data or we don't have the same context that is in Israel here in the U.S.A. And then I asked myself what happens if we approve -- if we say yes to this? How does it roll out? Will the people who have been vaccinated longest be the first to get the booster? I don't know who discusses that or who decides that.

I'm not comfortable with only using 12 people as an ends for the third booster in the clinical Phase III that we're being asked to evaluate, so I would like us to feel much more comfortable with what we're looking at from this clinical study in the USA with the differences we have in our population. What happens for people who did not get the Pfizer vaccine but have been vaccinated? There are too many questions for me to feel comfortable saying yes to this when I think with some more detailed study we can get some more answers. So what's happening with the clinical trials with others is my question.

DR. ARNOLD MONTO: Thank you, Dr. Fuller.

DR. OVETA FULLER: -- the ones that were enrolled in the clinical trials initially -- in the Pfizer clinical trial.

DR. ARNOLD MONTO: All right. Dr. Chatterjee.

DR. OVETA FULLER: Is there going to be an answer to that?

DR. ARNOLD MONTO: I think what we are going to do, Dr. Fuller, is to try to move early to a vote on

the question that is in front of us and then see where we go from there in terms of the session today.

DR. OVETA FULLER: All right. Thank you.

DR. ARNOLD MONTO: Okay? Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Yes. Thank you, Dr. Monto. I have several thoughts, but I will keep my comments to a couple of things that I don't think has been quite fleshed out by my colleagues. I agree with a lot of what's already been said. It seems to me -- and I'm taking Dr. Marks' suggestion to take all of the data into consideration -- that we do really have a very different situation in Israel than what we are facing here in the U.S. at this point in time. The data in Israel, particularly for those who are over 60, appear to me to be quite compelling for a booster dose in that population specifically.

But within the context of the U.S., I think that we're a large country. It's true. But there are also differences in different parts of the country that we're seeing, and there are parts of the country that are highly vaccinated. And they are not seeing break

through cases among those people who are highly vaccinated necessarily in those numbers. So I think that that's an important point to take into consideration.

And then finally, I want to go back to something that Hayley started off talking about and several other people commented on which is it is true that getting a larger gap between the prime and the boost whenever the boost might be does seem to be beneficial, and that's true for many vaccines. So would it then be beneficial to put that gap between the first and the second dose rather than to give a third dose booster after six months?

DR. ARNOLD MONTO: In other words, to summarize, there are a lot of questions to be answered after we take care of the issue in front of us, which is the booster vaccinations in those already vaccinated; correct?

DR. ARCHANA CHATTERJEE: Yes, thank you.

DR. ARNOLD MONTO: Okay. Dr. Pergam.

DR. STEVEN PERGAM: Thanks, Dr. Monto.

Certainly a lot of comments have been made. I'm happy to hear a lot of similar thoughts by my colleagues. I wanted to talk about the issue that Dr. Offit brought up. It's the issue of transmission. I do think it's important that -- with a large population in the United States vaccinated, that if we can decrease transmission, this could have some benefits for the pandemic in general and particularly in certain populations.

There's a lot of concern with healthcare workers of continued breakthrough for folks who are fully vaccinated, so that group that's been vaccinated very early. And because of strains on healthcare systems, that seems like an important issue that could be important. The challenge in front of us is that we're given this massive group to consider as the booster, and I think in many ways we'd like to be answering a separate question, which is kind of specifically high risk groups that we'd like to give the booster to. But that's not on our plate.

So I think it is important to consider

transmission and how this could have an effect. I agree that most of the transmission is happening in the mostly unvaccinated, but I think this can become more problematic if this trend does continue. And I would say in echoing something that Dr. Gans said, it felt like there were a number of comments during this discussion where people said, "There is a paper that is out. We'll be able to present this data to you soon, or it's coming next week." It feels like there's a lot of data that is circulating that could be helpful around this discussion that is not available at this moment, which makes it more difficult to make some of these decisions today.

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

DR. MELINDA WHARTON: Thank you. I really appreciate the comments from the other Committee members, and I agree with a lot of what's already been said. You know, it's a frustrating place to be in where we have in the United States more than adequate supplies of vaccine and yet have been unable to achieve the level of coverage that would result in much better

control of this pandemic than we currently have. So we're sort of in this position where we're having to think about administering third doses of the Pfizer vaccine, which is probably not the action that is going to have the most health impact in the United States.

Thinking about everything that's been presented, it does feel to me like benefits are likely for some part of the population, for people with underlying conditions, the immunocompromised people, the elder population. But I share the concern that's already been expressed by others about what we don't know about myocarditis in younger people. And given that the risk of breakthrough infection in that younger population is much lower than it is in other parts of the population, recommending a third dose for younger people is just not something I'd be comfortable with at this point.

DR. ARNOLD MONTO: Thank you, Dr. Wharton. Dr. Lee.

DR. JOOHEE LEE: So I just wanted to make a few comments. I think we -- to approve the vaccines to

begin with we had a lot of clarity on what we were supposed to be looking at -- a reduction of symptomatic COVID infection as well as the incidence of severe infection. It's not clear to me that the guidance is as clear cut here. It seems that the sponsor was giving some guidance with respect to the immunobridging studies that they appear to have met, but then there also seems to be a lot of -- we don't have a lot of data on the end points we had before as in the symptomatic infection after the booster shot and its improvement or any on the severe. It's much more limited.

And then a lot of discussion about transmission, which I agree is important, but we're sort of working without data in making those decisions. I'm also a little bit concerned that the study that we're looking at and the highest risk group we talked about, 65 and older as Dr. Fuller pointed, out only has 12 patients. I would agree that the Israeli data is really quite compelling. My enthusiasm is somewhat limited by the fact that the follow up period is less

than a month, so the sustainability is not yet clear. Thanks.

DR. ARNOLD MONTO: Thank you, Dr. Lee. Dr. McInnes.

DR. PAMELA McINNES: Paul, don't you think it's plausible that some people despite being fully immunized might not have a robust enough or a more efficient enough immune memory to rapidly mount a response when they see a variant that is like Delta, which has demonstrated not only really high transmissibility but very high viral replication? So I could imagine how if you didn't have sufficient circulating antibody and an antibody presence in the naris and maybe in the nasopharynx you could get overwhelmed with a virus like that. So I guess that they could be primed, but maybe you really need in certain people high levels of antibody presence because you may not have time to mount that response that you need despite being considered primed.

DR. ARNOLD MONTO: Dr. Offit, do you want to reply to that? Going a little out of order.

DR. PAUL OFFIT: That's a good question. So at the heart of that question is what's the incubation period, essentially, of serious disease? And so you're definitely right that if you have high titers of circulating neutralizing antibodies that's going to give you your best chance of decreasing the initial viral replication and even mild or moderate infection. Usually, as a general rule people believe that it takes a longer time to develop the kind of serious infection that gets you to the hospital -- I mean, a couple weeks. Which then means that you were -- if you have adequate frequencies of memory B and T cells, the activation differentiation time for that is usually about three to five days.

That's why the long incubation period diseases like measles, rubella -- you know, you can get essentially sterilizing immunity, and you can eliminate those diseases from your country, as we did actually with those two diseases earlier on. So I think I take heart in the fact that the incubation period is fairly long for serious infection, and therefore if you have

adequate frequencies of memory B and T cells, you're less likely to be overwhelmed. I'm sure you're right that there would be some cases where that incubation period is much shorter, but I think on balance it's generally long enough to allow activation differentiation memory B cells and T cells to protect. Thanks for the question.

DR. ARNOLD MONTO: Thank you. Dr. Sawyer,

DR. MARK SAWYER: -- the opinion that we need this in our armamentaria, a booster dose now, particularly for the elderly and other high risk conditions. But I share my colleagues' angst about the sparsity of safety data, and I am also anxious about the extrapolations both to older populations and younger populations. But we're not going to get a read on myocarditis until the vaccine booster is used extensively, and we have to rely on the VSD and other systems to capture that signal. And I'm sure they will be looking for it. So I'm hopeful that CDC rolls this out in a gradual fashion, but I think that I would be in favor of approving this because we are going to

likely need it for at least some of the population.

DR. ARNOLD MONTO: Dr. Pergam.

DR. STEVEN PERGAM: Apologies. My hand is still raised. I apologize about that.

DR. ARNOLD MONTO: That's okay. I was wondering. Dr. Portnoy.

DR. JAY PORTNOY: Great. Thank you. You know, it would be great to wait until we have all of the data about safety, but I work at a children's hospital. My hospital is filling up with kids who have COVID. We didn't want to rush into approve the vaccine for them, and now look where we are. It's very frustrating because we're just inundated with kids who supposedly weren't going to get COVID.

The concern that we have that people are going to get myocarditis from COVID vaccine is real. The question we really need to be asking, though, is whether it or any other severe adverse reaction from the vaccine is greater than the risk of getting it from breakthrough infection. Myocarditis is generally a short term condition. Most people who get it recover

from it. I worry more about long term systemic complications from COVID, which are real and can be prevented with the vaccine.

Look, antibody titers will help with systemic disease but not infections that -- just getting regular infections because that requires mucosal immunity. That's a different kind of immunity than what we're getting from a systemic vaccine. We really have two diseases, a mucosal disease and a systemic disease. Mucosal is how it spreads. That's why people who have been vaccinated can still get the disease.

They get it in their nose. They spread it. They don't have secretory IGA because it was injected into their muscle, and that doesn't induce an IGA response. Systemic COVID results in hospitalization and long term morbidity. So that's what I think we should really be concerned with.

Immunity clearly seems to decrease over time. We saw that with the data from the United States, also from the Israeli data. Do we want to wait until more previously vaccinated people get sick before we prevent

them from getting sick? As one of those people who are at risk, I've had two vaccines. I'd rather not get the COVID disease. I'd rather get the third vaccine.

My wife already got her third dose. I plan to do the same thing next week. Pharmacies are giving it out off label. I would really love to be able to get it and prescribe it on label rather than have to do it off label because we refuse to recommend approval. So I'm strongly in favor of approving this vaccine.

DR. ARNOLD MONTO: Dr. Levy.

DR. OFER LEVY: Hi, Dr. Monto. Thank you for all that, and we saw the question as carefully phrased by FDA to us. And I'm sure the decision will be to have us vote on the question as phrased. My question is given the number of Advisory Committee members who are expressing similar concerns, if the motion doesn't pass as written, will there be opportunities to propose a modification?

DR. ARNOLD MONTO: Dr. Marks.

DR. PETER MARKS: The answer to that is yes.

DR. ARNOLD MONTO: While you are on, where

should we be explaining our votes? Should we explain the votes after we have the vote? Would that be of help in determining the question?

DR. PETER MARKS: Yeah. Dr. Monto, I think perhaps for efficiency it may be worthwhile going around the Committee to just get a sense of the Committee of where people are, and then perhaps we can take a moment and ensure that what we then come back to you with for a vote makes some sense if you're willing to do so.

DR. ARNOLD MONTO: I'm perfectly willing to do so. So in other words we don't have to have a vote on that question?

DR. PETER MARKS: I would say that for right now maybe we could go through and get a sense of where the Committee stands, and rather than going to vote on that question if the Committee decides that they'd like to, we can then see where we stand about putting that question forward.

DR. ARNOLD MONTO: Dr. Marion Gruber?

DR. MARION GRUBER: Yeah. I just wanted to

make the point that Pfizer has submitted a supplemental BLA asking to get an additional indication for a booster dose when administered six months after the primary series for individuals 16 years of age and older. And I believe that we do need a vote on this question.

DR. ARNOLD MONTO: And I think we can do that efficiently, which may be quicker as a matter of fact than going around the table. So what I would propose is that we do have the vote, and then we can go around the table and discuss where we think a modification would be necessary or approvable. How about that? Hearing no -- Dr. Marks?

MR. MICHAEL KAWCZYNSKI: Make sure you're unmuted, doctor.

DR. PETER MARKS: Yes, thanks. Please feel free to move ahead to a vote. I think we'll go with what Dr. Gruber has suggested when we can have your explanations, and then we can move appropriately thereafter. Thank you.

DR. ARNOLD MONTO: Okay. Do any --

MS. DONNA BOYCE: Dr. Monto?

DR. ARNOLD MONTO: Yes?

MS. DONNA BOYCE: I'm sorry to interrupt. Is it possible for Pfizer to make any final statements since we kind of had many technical issues and actually weren't able to address many of the questions? We will be brief.

DR. ARNOLD MONTO: Okay.

MS. DONNA BOYCE: Thank you.

DR. ARNOLD MONTO: I'll give Pfizer five minutes to make final statements as long as we can hear you. Otherwise we'll stop.

MS. DONNA BOYCE: I'll do my best. All right. Dr. Bill Gruber, please comment. Go ahead. The floor is yours.

MR. MICHAEL KAWCZYNSKI: Who's supposed to be speaking here?

MS. DONNA BOYCE: Bill Gruber.

MR. MICHAEL KAWCZYNSKI: He's coming. Okay.

DR. BILL GRUBER: Can you hear me? Okay. Let me run next door.

MR. MICHAEL KAWCZYNSKI: Yes, we can.

MS. DONNA BOYCE: He's here.

DR. BILL GRUBER: Sorry, I had to run from another room. My apologies for holding up the Committee.

DR. ARNOLD MONTO: We can hear you.

DR. BILL GRUBER: Okay. That's good. We solved at least that problem. So again, I think we're all centered around the same goal here, and that is to make a safe and effective tool available to the maximum population that stands to benefit. So we're obviously eager for the Committee to vote on the existing question, and we hope they will keep that in mind.

I think there have been a lot of issues that surround the rare risk of myocarditis that is already in the existing label. As you heard from Dr. Sawyer -- and I think this is an important piece -- it's unlikely that we'd be able to identify myocarditis in clinical trials. We weren't able to identify that obviously in the circumstance of the original licensure. It was only with the intense pharmacovigilance that occurred

after the fact, and I think it's encouraging to me -- and I hope to the Committee members -- that the Israeli data, although it's not a full month out -- it spans the time when myocarditis is most likely to occur based on their own data and based on what's seen by the CDC. So the expectation, I think, is that this is going to be a rare event, just as it was after the first two doses, and will only be determined by pharmacovigilance.

So in thinking about this -- and I don't know whether there are CDC members that would want to comment on this -- but the published data has made very clear that the risk-benefit profile all the way through the age ranges, whether we're talking about young adolescents, 16 to 17 years of age, or we're talking about individuals older, the risk-benefit is clear. In fact, there seem to be more cases of myocarditis in some of those age groups with COVID-19 then there are with the vaccine. And then if you add to that the hospitalizations, the illnesses, the need to essentially stop the pandemic before we continue to

generate variants -- so I think the bottom line is the balance of evidence supports a broad recommendation.

But we welcome the Committee's voting on the current question but then certainly not depriving the ACIP or other recommending bodies the opportunity to make a decision about how the vaccine can be best used. The first goal is give the tool to those recommending bodies so they can best apply how the vaccine might be used.

DR. ARNOLD MONTO: Dr. Cohn, would you like to respond on behalf of the CDC? And then we're going to vote.

DR. AMANDA COHN: Sure. Thanks. I just want to clarify Pfizer's comments that the risk-benefit analyses that have been done have compared the risk of an adolescent not being vaccinated at all to having two doses, and that risk-benefit is in favor of vaccination. But the incremental benefit of a third dose over a second dose has not been presented or completed yet, so I just don't want the Committee members to get confused with the incremental benefit of

a third dose and the comparative risk of double exposure to both a second and potentially an additional risk with that third dose.

DR. ARNOLD MONTO: Thank you. Prabha and Kathleen, are we ready to have a vote?

MS. KATHLEEN HAYES: Yes, we are.

DR. ARNOLD MONTO: And we are voting with the proviso that we are going to have further -- an explanation vote and potentially further voting thereafter.

MS. KATHLEEN HAYES: Understood. Can you hear me fine?

DR. ARNOLD MONTO: Yes.

MS. KATHLEEN HAYES: Okay. Great. So, Mike, can you pull up the --

DR. ARNOLD MONTO: He's got the question in place.

MS. KATHLEEN HAYES: Okay. Thank you. So just for a note, only our members and temporary voting members, excluding the industry representatives, are going to be voting. Dr. Monto can read the question

for the record, and then afterwards all members and temporary voting members will cast their vote by selecting yes, no, or abstain in the voting pod. You'll have two minutes to cast your vote once the question is read, and then after all the votes have been placed, we will broadcast the results and read the individual votes allowed for the record.

Please just note that once you cast your vote, you may change your vote within the two minute timeframe. However, once the poll has closed, all votes are considered final. Unless anyone has any questions, Dr. Monto, if you could please read the voting question.

DR. ARNOLD MONTO: All right. And the voting pod is not there yet but let me read the question first. Do the safety and effectiveness data from the clinical trial support approval of the Comirnaty booster dose administered at least six months after completion of the primary series for use in individuals 16 years of age and older?

MS. KATHLEEN HAYES: Thank you. And Mike, can

we pull up the voting pod? Okay. We have the voting pod up, so go ahead and cast your votes at this time, please. We're still getting votes in, so we've got about a minute remaining for individuals to cast their votes. Okay. It looks like we've received all of the votes. Let me read them aloud for the record. There should be 18 total votes today. Dr. Cohn has a no vote.

DR. PRABHAKARA ATREYA: We have 19 here in the pod, Kathleen.

MS. KATHLEEN HAYES: Right. We will figure out where the additional vote came in. So if we can close the poll, I'm going to read the votes aloud. Dr. Cohn voted no. Dr. Portnoy voted yes. Dr. Lee voted no. We did have an accidental vote from a speaker, so that will be disregarded. Dr. Chatterjee voted no. Dr. Perlman voted no. Dr. Gans voted no. Dr. Meissner voted no. Dr. Levy voted no. Dr. Hildreth voted no. Dr. Wharton voted no. Dr. Fuller voted no. Dr. Kurilla voted no. Dr. Monto voted no. Dr. McInnes voted no. Dr. Rubin voted no. Dr. Pergam voted no.

Dr. Sawyer voted yes. Dr. Offit voted no. So this vote did not pass since the majority voted no. Thank you. Dr. Monto, I will hand it back to you if you wanted to go around the table.

DR. ARNOLD MONTO: Right. Now, let's clear the raised hands, and what we will now do is for those who wish to explain their vote and to propose something that they might be in favor of, let's take this up as the next question. So, Dr. Lee, is that your hand (audio skip).

DR. HAYLEY GANS: You called my name.

DR. ARNOLD MONTO: I did. I wasn't sure if (audio skip).

DR. HAYLEY GANS: Okay. Thank you. Thank you for allowing us to have this opportunity just to think through what maybe next steps are. And I think, you know, a lot of the concerns were articulated very well previously. I think that a lot of individuals do feel that there is a role for another dose in populations, and we would like to see that come forward.

We would also like to see some of the -- we

don't need it from the very small data set that was done in this third dose from Pfizer, but we really do need the broader safety data that's already available to bring this question, again, further to other populations that are in question still. So I think I would support having a third dose available for other high risk groups that weren't already given a third dose, such as individuals over the age of -- to something, 50 to 60 -- there's different studies out there -- and then looking more closely at the safety data for those other individuals. And I would also like to know about --

DR. ARNOLD MONTO: I'm going to make it difficult for the speakers and ask them to come up with an age that they would feel comfortable with. You can always change your mind afterwards, but we need to start somewhere.

DR. HAYLEY GANS: Okay. All right. I would love to see something greater than 50, and I would also like to see data on the decrease in ability to spread the virus to those who are not able to get vaccinated.

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

DR. ARCHANA CHATTERJEE: Yes, thank you, Dr. Monto. I echo what Hayley said, but I do want to explain my vote. I have major concerns with regard to the extrapolation of data from much older populations to 16 and 17-year-olds. We have no data on the safety in this population at all that have been presented so far, and that concerns me significantly. I also think that the safety database that has been presented is too small.

In terms of the benefits to clearly an older population as I mentioned early, I think the Israeli data are very compelling for those over 60. I also noted that in most of the presentations there was a big gap in people who are between 55 and 65. They were missing in the analyses. So I would say I'd like to see more data before I would recommend it for a younger age group, but over 60 is probably okay from my standpoint.

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

DR. MICHAEL KURILLA: Thank you, Arnold.

Yeah, agreeing with my colleague. I think the safety database is inadequate, particularly in the populations that I really would like to see a boost that might be much more appropriate. The effectiveness data is pretty much limited to boosting antibody levels, and without a very good correlative protection, we can't really evaluate how effective that's going to be. I also agree with the CDC that the incremental benefit to the younger population really has not been demonstrated at all.

And as I questioned the CDC earlier this morning, as the background rate of natural infections continues to increase in the population, the ability to actually discern the vaccine efficacy is going to look less effective over time just because of the high rate of prior natural infections that are occurring. So I think this needs to be teased out very carefully. I think we need to target the boosters right now specifically to the people are likely to be at high risk, and it's an older population. It's immunocompromised. I think if I wanted to include

obesity, it'd probably be at a BMI of at least over 35 or something like that -- people with diabetes, clearly all of the high risk factors that have been identified for serious COVID disease because I think ultimately that's what we're trying to do is to prevent the serious disease.

I agree with my colleagues that reducing transmission is a very laudable goal. Ideally, we'd love to have a sterilizing -- we'd love to have sterilizing immunity. But I haven't seen any data to really address that one way or the other, so I don't know how we would approve boosters on an expectation that transmission would be reduced at this point. So I think we need to target where we're going to do boosters and continue to examine the potential efficacy of boosters in a broader population.

DR. ARNOLD MONTO: Thank you, Dr. Kurilla. Dr. Offit.

DR. PAUL OFFIT: If I had to pick an age, by the way, I would pick 65. But one thing I would love to have -- and I guess I challenge Amanda Cohn and

Melinda Wharton with this -- I would love to see the CDC provide data to answer the following question. Is it possible to get control of this virus? Meaning to provide a significant enough level of herd immunity that there's dramatic decrease in transmission than hospitalization and death with two doses.

So if you look at those countries or regions or states that have very high immunization rates in certain regions, do we dramatically reduce the instance of hospitalization? In other words because we're not going to be great at preventing asymptomatic infection. We're not going to be great at preventing mildly symptomatic infection. I really wish we didn't use the term "breakthroughs" there because if that's true, then pretty much every vaccine that we have has at some level breakthroughs.

I mean, the rotavirus vaccine that we worked on was not very good a preventing asymptomatic or mildly symptomatic infection, but it was very good at preventing moderate to severe disease. And so now residents don't see rotavirus disease anymore. I'm

glad they never called asymptomatic or mildly symptomatic rotavirus infection breakthroughs.

So that's my question to the CDC. Can you get control of this infection with two doses? What is the evidence of that? Because if you can't, then that makes a compelling case for the third dose.

DR. ARNOLD MONTO: Dr. Cohn, do you want to answer that question? And what do you think the Israeli data with the high vaccination rates there contribute?

DR. AMANDA COHN: Thanks, Dr. Offit. I am not -- I don't have the data or the ability to answer that question completely right now. What I can say is at this moment it is clear that the unvaccinated are driving transmission in the United States, and when we look at modeling, for example, in congregate settings, it's frequently outside community transmission and unvaccinated individuals that contribute to increased cases in the United States at this time, which I will caveat that with.

I also think that other interventions such as

social distancing and masking will have to be part of the solution. Vaccination will never be perfect. But I do believe that a third dose at some point in time -- maybe not right now. Maybe for groups of people who were vaccinated early right now -- will contribute to additional reduced transmission, especially in states and communities that do have high coverage and are still seeing cases. So it does make sense from the perspective of you need high protection and given the differences in time in which we've vaccinated since last December until people really just getting vaccinated now, that people who were vaccinated a long time ago and who maybe have lower antibodies now -- the boost will presumedly prevent some additional transmission. But we really can't answer that with data right now.

DR. ARNOLD MONTO: What do you think the Israeli data and the Provincetown data tell you, Amanda?

DR. AMANDA COHN: So I think that the Israeli data is very compelling. I think that we need a little

bit more time. I totally believe that a booster dose will provide protection against disease and potentially even infection in individuals for a period of time. But I think we would prefer to see six weeks out or, you know, (Inaudible) out over a longer period of time to have real evidence that the booster dose is contributing to reduced transmission in their overall population.

DR. PAUL OFFIT: One quick question, it's certainly true that for a vaccine like this it's not surprising that neutralizing antibodies will decline over time, and so we give a booster dose. It is also, therefore, very likely that over time the booster dose and the increased antibodies will also decline over time. So are we talking about, then, annual, biannual, triannual booster doses? Because I know that we've heard two things. We've heard, one, booster dosing more frequently, and, two, that this is a three dose vaccine and then we're done. I mean, how do you see it, Amanda?

DR. AMANDA COHN: Yeah, I believe --

DR. ARNOLD MONTO: I'm not going to -- let's not even speculate about that. I have my own opinion, and probably Amanda has her own opinion. But that's not the question we're being asked today, so let's focus on where we are today. And let's hear from Dr. Perlman.

DR. STANLEY PERLMAN: Yes. So I just wanted to make a couple of extra points. So first, I think when we talk about transmission, there's many studies that show in fact that if we really want to deal with transmission we probably need to do something like deliver vaccine intranasally to actually prevent infection at that site. And that's mostly pre-clinical, but that certainly makes sense. It has been said by other speakers.

The second thing is that when we talk about age, I also agree that this should be around 60. Others have said different ages around there, but the group that I worry about that's not included in over 60 and doesn't have comorbidities are healthcare workers because the system is so overstretched now that we

can't even have healthcare workers get mild infections or be positive because by staying home that puts even more of a risk on the failure of the whole system. So I don't know how we put that into our equation, but I think that that's a group that we have to consider as being possibly a candidate for a third vaccine.

DR. ARNOLD MONTO: Thank you, Dr. Perlman. That's very helpful. Dr. Pergam.

DR. STEVEN PERGAM: Dr. Perlman stole my thunder with that comment. I think he's absolutely on target. I'm very concerned about healthcare systems. They're already overstretched and many of which are unable to find additional people to fill in gaps. If we continue to have even mildly symptomatic infections, it will actually put many healthcare systems in trouble.

I think healthcare workers have to be considered as a potential population to be offering third doses because we don't have a lot of capacity, and we can't be losing people in hospitals to illness which will take them out for a minimum of 10 days in

most of the situations. And a large outbreak in a hospital system can be quite problematic, so I think we have to strongly consider that group. And I'd be comfortable with people 60 and older being another additional group that could get boosters beyond that.

So I actually think the way that the ACIP had laid out how they might approve this looked feasible to me. And the groups that were the highest risk were nursing home residents, people that were 65 and older, and then healthcare workers would be the group that I'd be most comfortable with approving for a booster.

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

DR. OFER LEVY: Hi. Thank you for that. I agree with some of the other Committee members who mentioned that a third dose is likely beneficial. That's already true for the immunocompromised. It's likely beneficial, in my opinion, for the elderly and may eventually be indicated for the general population. I just don't think we're there yet in terms of the data.

As other Committee members have pointed out,

more needs to be known about the correlates of protection, both antibody and cell mediated. We are in an era of precision vaccinology. That's the basis of our precision vaccine's program.

We need age specific data. The risks for various adverse events vary with age, and therefore the data presented to our Committee should mirror that age group if we're asked to vote in favor of use in that age group. And we also would like to see some data on the impact on transmission.

Finally, in terms of a revised question, I would advocate for one that's phrased for ages 65 and up. That's an age group where more severe COVID is seen, and that could be one way to phrase the question, although 60 and up also matches the compelling data from Israel. So those are my opinions. Thank you.

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

DR. ERIC RUBIN: I'm 63, so I like the 60 age instead of the 65 age. And I think for just exactly the reasons that Ofer just mentioned, that the safety data we have reflects 60-year-olds. I think it would

be great if we could give a sort of less restrictive language to the rest of it, though, and offer it to people who are at higher risk of disease. That could be higher risk of developing severe disease because of their risk factors or higher risk because of exposure, such as healthcare workers.

And the reason is we don't -- that's quite a bit different from saying people should get a third dose because that gets closer to it being written in as a mandate, that everyone should get it. And I think none of us are ready for that -- or few of us are ready for that right now. It would be much easier to give practitioners the ability to give doses to people they think really need them based on the data that are out there, and they're rapidly changing right now -- by next week as people have pointed out. Some of these things in pre-print are actually likely to be out.

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

MR. MICHAEL KAWCZYNSKI: Dr. Monto?

DR. ARNOLD MONTO: Yes.

MR. MICHAEL KAWCZYNSKI: We're getting a lot

of questions coming in, so, Kathleen, can you please go over the vote total? People are wondering why there was an extra vote, and we want to make sure everybody online also understands why. So Kathleen, are you there?

MS. KATHLEEN HAYES: Yeah. I'm here. Sure I can help clarify. We just had one speaker accidently vote, but the final vote was two yeses and 16 no votes. Thank you.

MR. MICHAEL KAWCZYNSKI: Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Meissner who surprisingly is the last one to have his hand raised. And would the FDA staff be ready for me to ask what they would propose as the next voting question after we hear from Dr. Meissner?

DR. PETER MARKS: We'll be ready as soon as Dr. Meissner's done. Thank you.

DR. ARNOLD MONTO: All right. Thank you.

DR. CODY MEISSNER: Thank you, Dr. Monto.

DR. ARNOLD MONTO: You're up, Cody. We heard you.

DR. CODY MEISSNER: Is this okay?

DR. ARNOLD MONTO: Yeah. We hear you.

DR. CODY MEISSNER: Yeah. Okay. I'd just like to express a few thoughts. First of all, as has been stated I don't think a booster dose is going to significantly contribute to controlling the pandemic. And I think it's very important that the main message that we still transmit is that we've got to get everybody two doses. Everyone has to get the primary series. This booster dose is not going to make a big difference. It's not likely to make a big difference in the behavior of this pandemic.

Secondly, again, I agree with what Dr. Marks said earlier that this is a killed vaccine, and our experience with killed vaccines is quite clear that we need to have doses six months or longer apart in order to ensure protective immunity. But one of the questions -- I think it's going to be very hard to do with the trial, but if we could separate the distance -- the length of time between the first dose and the second dose, it might not be necessary to give a third

dose. I don't know how we'll be able to go about addressing that issue. But I think that deserves some consideration.

And then thirdly, in terms of the people who have risk factors such as obesity my thinking is that that should apply to people under 65 year of age. I mean, there are clear risk factors -- groups who fall into the risk of hospitalization and more severe disease who are under 60 or 65. It seems to me we should probably include them in consideration of a booster dose, and I'll stop at that point. Thank you.

DR. ARNOLD MONTO: Thank you, Cody. And Dr. Marks.

DR. PETER MARKS: I believe we've been getting ready a revised voting question, but while we're getting that together for you, I believe hearing what you've been saying what we would probably suggest is something along the lines of "Based on the totality of scientific evidence available, including the safety and effectiveness data from clinical trials C459001, do the potential benefits outweigh the potential risks of a

Pfizer-BioNTech COVID-19 mRNA vaccine booster dose administered at least six months after completion of the primary series for use in individuals 65 years of age and older and those judged to be at high risk of complications due to occupational exposure or underlying disease?"

DR. ARNOLD MONTO: Thank you. Question of Prabha and Kathleen, do we need that in writing before we vote? And if so, should we take a break?

MS. KATHLEEN HAYES: Dr. Atreya, I think we can get the question ready in the voting pod. Are we okay to do that or -- Dr. Atreya, I think you're muted.

DR. ARNOLD MONTO: Dr. Marion Gruber, do you have a comment?

DR. MARION GRUBER: Yeah. I just wanted to make a suggestion. While we actually put the slide together as suggested by Dr. Marks, can we take a short break to get this right? And also because it is now an EUA that is on the table, we could also remind the Committee (Inaudible) if that's what people think. We don't need these discussion questions any longer.

DR. ARNOLD MONTO: Okay. Let's take a break, then, for -- is five minutes enough or 10 minutes better?

DR. MARION GRUBER: Maybe 10 but not more than 10 minutes.

DR. ARNOLD MONTO: Okay. 10 minutes. We'll reconvene at five minutes after 4:00 Eastern.

DR. MARION GRUBER: Thank you.

(**BREAK**)

DR. ARNOLD MONTO: Home stretch.

MR. MICHAEL KAWCZYNSKI: All right. Welcome back and thank you for allowing us to do that little break. We are all set. So, Dr. Monto, if you want to take it away.

DR. ARNOLD MONTO: Yes. I'd like to call on Dr. Fink from FDA who is going to tell us about the next steps.

DR. DORAN FINK: Thank you. So following the vote for our first voting question, FDA recognizes that

the Committee had several concerns, one concern related to benefit-risk balance in the general population of individuals 16 years of age and older and a second question related to the data and level of evidence to support the safety and effectiveness of a booster dose. And so in response to these concerns, FDA has formulated a second voting question, and I want to make clear that the second voting question involved emergency use authorization rather than approval or licensure, which was the subject of the first voting question.

So I'd like to spend just a few moments reminding the Committee of some principles around emergency use authorization. These slides were previously presented in the October 2020 VRBPAC meeting. So here on this slide are the statutory criteria for FDA issuance of an emergency use authorization. First, the agent referred to in the emergency use authorization declaration can cause a serious or life-threatening disease or condition. We know this to be true for SARS coronavirus-2.

Secondly, the medical product may be effective to prevent, diagnose or treat the serious or life threatening condition caused by the agent. Third, the known and potential benefits of the product outweigh the known and potential risks of the product, and the second and third criteria are tied together in an overall benefit-risk assessment. And finally, that no adequate approved and available alternative to the products for diagnosing, preventing, or treating the disease or condition. So in this case we are talking about the potential for emergency use authorization of a booster dose of the Pfizer-BioNTech COVID vaccine that is not currently available. Next slide, please. May I have the next slide, please? Thank you.

So issuance of an EUA for a COVID-19 vaccine or in this case for a booster dose of a specific COVID-19 vaccine will specify the conditions for use in which benefit-risk has been determined to be favorable based on the review of the totality of available data. And these conditions include the population to be included in the emergency use authorization, the conditions for

vaccine distribution and administration, and requirements for safety monitoring and reporting of adverse events. For this specific proposed emergency use authorization, we would expect that the conditions for distribution and administration and requirements for safety monitoring and reporting of adverse events would remain the same as in the current emergency use authorization for the vaccine.

Secondly, the emergency use authorization will provide information to vaccine recipients and healthcare providers by way of prescribing information and factsheets that describe the investigational nature of the product, the known and potential benefits and risks, and available alternative and the option to refuse vaccination. So what we're talking about here is a revision of the current factsheets for vaccination providers and vaccine recipients and their caregivers. Next slide, please.

I also want to remind the Committee that issuance of an EUA for any product, including the COVID-19 vaccine or a booster dose of this specific

COVID-19 vaccine, may be revised or revoked if circumstances justifying the emergency use authorization no longer exist, if criteria for issuance are no longer met -- i.e. the statutory criteria on the first slide -- or if other circumstances arise that warrant changes necessary to protect public health or safety, such as those based on new information concerning vaccine safety, vaccine effectiveness, vaccine manufacturing or quality, or a new information about COVID-19 epidemiology or pathogenesis. Next slide, please.

So this is the voting question number 2 that we will ask the Committee to consider. Based on the totality of scientific evidence available, including the safety and effectiveness data from clinical trial C4591001, do the known and potential benefits outweigh the known and potential risks of a Pfizer-BioNTech COVID-19 vaccine booster dose administered at least six months after completion of the primary series for use in individuals 65 years of age and older and individuals at high risk of severe COVID-19? That was

the end of my presentation. Thank you.

DR. ARNOLD MONTO: Thank you, Dr. Fink. What I am proposing is that we move directly to this voting question. We've already had a lot of discussion. And then for anybody who wants to explain their vote, we will go on to explanation of votes before we adjourn. So the voting question -- should I be reading it for the record?

MS. KATHLEEN HAYES: Please. Thank you.

DR. ARNOLD MONTO: Based on the totality of scientific evidence available (audio skip)

MS. KATHLEEN HAYES: Dr. Monto, I can't hear you. Did we lose your audio?

MR. MICHAEL KAWCZYNSKI: I think we did lose Arnold. I don't know. Yeah, I think he hung up accidentally. Yeah. He noticed it. Just a moment. Yeah, we saw that. We'll just let you start again.

DR. ARNOLD MONTO: Can I go ahead?

MR. MICHAEL KAWCZYNSKI: Yeah. Go ahead.

DR. ARNOLD MONTO: Yup. Have you got me?

MR. MICHAEL KAWCZYNSKI: Yeah, we do, sir. Go

ahead.

DR. ARNOLD MONTO: Okay. We were doing too well in terms of the technology. So do the known and potential benefits outweigh the known and potential risks of the Pfizer-BioNTech vaccine booster dose administered at least six months after completion of the primary series for use in individuals 65 years of age and older and individuals at high risk of severe COVID-19?

MS. KATHLEEN HAYES: Thank you, Dr. Monto.

MR. MICHAEL KAWCZYNSKI: Yeah, we have it. So again, to all my members, please make sure -- you control your own muting. Please make sure you are muting yourself. All right. Kathleen Hayes, take it away.

MS. KATHLEEN HAYES: Yeah. Thank you, Mike and Dr. Monto. So same process as the first voting question. When you see the voting pod come up, please select yes, no, or abstain. Then you will have two minutes. And just as a reminder only voting members and temporary voting members can vote. Thank you. Go

ahead. Okay. That was pretty quick. It looks like all of the votes are in, so we can close the poll.

And we do have a unanimous 18 out of 18 who voted yes for this question. And I will read the votes aloud for the record. Dr. Cohn, yes; Dr. Portnoy, yes; Dr. Lee, yes; Dr. McInnes, yes; Dr. Perlman, yes; Dr. Gans, yes; Dr. Meissner, yes; Dr. Chatterjee, yes; Dr. Hildreth, yes; Dr. Wharton, yes; Dr. Fuller, yes; Dr. Kurilla, yes; Dr. Levy, yes; Dr. Offit, yes; Dr. Rubin, yes; Dr. Pergam, yes; Dr. Sawyer, yes; and Dr. Monto, yes. So thank you for your votes, and I will hand it back to Dr. Monto.

DR. ARNOLD MONTO: Okay. Explanation of votes for those who have raised their hands. Cody Meissner.

DR. CODY MEISSNER: Dr. Monto, can you hear me?

DR. ARNOLD MONTO: Yes.

DR. CODY MEISSNER: I would just like to ask Dr. Fink one question. So the second bullet will apply to everyone who is 16 years of age or older that is at high risk; is that correct?

DR. DORAN FINK: Yeah. The second bullet would apply to individuals for whom the vaccine is authorized who are at high risk of severe COVID-19.

DR. CODY MEISSNER: Thank you.

DR. ARNOLD MONTO: Dr. Pergam.

DR. STEVEN PERGAM: Thanks, Dr. Monto. I think my only -- I voted yes on this. My only concern was the comment of high risk severe COVID-19 because I do think this will potentially put healthcare workers in a different situation. They're not necessarily at risk for severe COVID but for developing COVID. So I just want to reiterate that I think that healthcare workers are a particularly high risk group for acquisition as the antibodies wane, and we have not addressed that in this particular statement.

DR. ARNOLD MONTO: Thank you, Dr. Pergam. I just want to remind the Committee that the ACIP will be meeting to fine-tune some of our recommendations. Dr. Sawyer?

DR. MARK SAWYER: I just wanted to explain both my votes since I voted yes on the first question,

on, of the distinct minority. Are you hearing me okay? My camera's not working for some reason.

DR. ARNOLD MONTO: Yes. We hear you loud and clear.

DR. MARK SAWYER: Okay. So I voted yes on the first question because I thought it was the quickest, most efficient way and most flexible way for providers to be able to target certain populations, but I'm certainly comfortable with this as long as the ACIP provides enough additional guidance about exactly who we think are most concerning.

DR. ARNOLD MONTO: Dr. Portnoy.

DR. JAY PORTNOY: So you're inviting the two yes speakers from the previous question to address each other one right after the other.

DR. ARNOLD MONTO: It was just chance.

DR. JAY PORTNOY: Okay. Well, both of my answers are kind of like what we just heard. I think that it's great that this becomes available because this vaccine is something that I think really has an opportunity to stem the COVID epidemic. Healthcare

workers are at high risk of catching COVID. They're not at risk of severe COVID, but we're at risk of spreading it to our patients. So I think it's really important that we not get infected.

The most dangerous thing is asymptomatic infection. If you get infected with COVID and you don't know you have it, you're more likely to spread it. And that's what the doubly vaccinated people are most at risk of having. So I think it's really important that we consider that when we decide about approval. But I'm really glad that we authorized this vaccine for a third dose, and I plan to go out and get my third vaccine this afternoon. Thank you.

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

DR. MICHAEL KURILLA: Thank you, Arnold. I guess my camera isn't working again either. Yeah, I just wanted to say that I really appreciate the rewording of the question. I think it more targets what the available data that we have where a booster dose is going to be likely to be most effective. I think it does highlight, though, in a lot of the

discussion we had some of the outstanding questions that still remain, and the vaccine manufacturers and the academic community really need to be focused on addressing some of those.

Transmissibility and the relationship between vaccination and the number of doses I think is a very important question, and really understanding the true correlates of protection and how that's informed durability assessments going forward I think still remain an open question. We just can't simply be in a position where we would just be vaccinating people every time we think there's a problem, so we really need to get a better handle on understanding exactly how these vaccines are mediating protection and the durability of that protection. Thank you.

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

DR. STANLEY PERLMAN: Yeah. I just wanted to extend the question that Dr. Pergam raised. So at the ACIP meetings, can they consider basically the use of the vaccine in a group that wouldn't necessarily be under these two categories? So the idea with the

healthcare workers not being in either one, I believe you said that the ACIP could still include them. But can they include them if it's not in these categories that the FDA may approve?

DR. ARNOLD MONTO: Thank you, Dr. Perlman. The next one who has raised her hand is Dr. Cohn who maybe -- or Dr. Marks. Would you like to jump in?

DR. PETER MARKS: This is Dr. Marks. I'd very much like to jump in here. We are not bound at FDA by your vote, just so you understand that. We can tweak this as need be, and I would ask formally, Dr. Monto, without further ado from anyone else from FDA jumping in, for you to poll the members as to whether or not healthcare workers be included or not in this or whether there's any other risk group that they would like to.

We do not have to take a vote on that question. We will take that back, and then we can refine this question as we need it based on the members. So this is not a voting question, but I am requesting that you ask all 18 members and tell us how

they might further refine this in any way. We would really appreciate that because that is why we moved to this kind of a pathway because we have more flexibility. Thanks very much.

DR. ARNOLD MONTO: Okay. We need instructions as to how to be polled rather than asked a question.

MR. MICHAEL KAWCZYNSKI: Dr. Monto and Prabha, I can put up what we call a short answer with the question being, and we'll clarify the question. How should we further refine -- and, Dr. Marks, what were you asking?

DR. ARNOLD MONTO: Instead of that, let's ask the question should healthcare workers be included in this EUA.

DR. PETER MARKS: That's fine by me, Dr. Monto. That's fine.

DR. ARNOLD MONTO: I'm always against open ended questions.

MR. MICHAEL KAWCZYNSKI: Okay. Before anybody vote, I'm just going to -- hold on.

DR. AMANDA COHN: Peter, his is Amanda. Could

I suggest even some language like "people at high risk for occupational exposure" as opposed to even just --

DR. ARNOLD MONTO: Okay. Let's do that.

UNIDENTIFIED MALE: I totally agree with Amanda because I think we'd be leaving a lot of people out if we did just healthcare workers.

DR. PETER MARKS: I want to make sure that the Committee understands when we're saying people at high risk for occupational exposure, what we will be taking that to mean at FDA is healthcare workers, frontline workers such as teachers and potentially essential infrastructure workers as well. Is that what we're thinking there?

DR. ARNOLD MONTO: Yes.

DR. PETER MARKS: Okay. Thank you.

MR. MICHAEL KAWCZYNSKI: Okay. So I just want to make sure I captured what Dr. Cohn said. You said should healthcare workers and somebody else be included in this EUA. What was the other one?

DR. PETER MARKS: Amanda, I think you had it very nicely formulated. If you could just say it

slowly so that it can be captured. Thank you.

DR. AMANDA COHN: I think it's individuals at high risk for occupational exposure.

MR. MICHAEL KAWCZYNSKI: All right. I'm just going to check this real quick. Kathleen --

UNIDENTIFIED MALE: I do have one question, though. Why does it have to be occupational exposure? Can't it just be any exposure? Does it have to just be part of their job?

DR. ARNOLD MONTO: I think that's a can of worms, frankly.

MR. MICHAEL KAWCZYNSKI: All right. So, Dr. Marks and Dr. Monto, if you would please check what I put on there?

DR. ARNOLD MONTO: I think that that really makes it very difficult to interpret because anybody could be at high risk if you have a child who's in school. You might consider yourself being at high risk, so I would prefer leaving it as occupational exposure.

MR. MICHAEL KAWCZYNSKI: Okay. So right now

this is -- again, this is not a voting question. This is just a question to the Committee.

DR. PETER MARKS: Hold on. I just want to make sure we just get -- it looks like to me there's may be a parsing error because it's should healthcare workers or others at high risk of -- because I think that is what was added there. It wasn't just healthcare workers. It was other individuals. Is that correct, Dr. Monto?

DR. ARNOLD MONTO: Yes, that is correct.

DR. PETER MARKS: And there's an "R" missing from workers. Spelling is not my strong suit, but actually that one I caught.

MR. MICHAEL KAWCZYNSKI: That one I caught, too. Yeah. There we go. Should healthcare workers or others at high risk for occupational exposure be included in this EUA? Okay. Again, this is not a voting question. Dr. Atreya or Kathleen --

UNIDENTIFIED FEMALE: Could you fix the spelling on healthcare, please?

MR. MICHAEL KAWCZYNSKI: Hold on. I can't

even see what I'm typing here.

DR. PETER MARKS: It's a long day, but we're not looking for people who are doing gardening.

MR. MICHAEL KAWCZYNSKI: There we go. Okay. I think we're good.

UNIDENTIFIED MALE: Will ACIP further define these groups?

DR. PETER MARKS: That's certainly within their purview that they could do that.

MR. MICHAEL KAWCZYNSKI: Now, this is not a voting question. Again, this is just you are polling the Committee. Am I correct? Kathleen?

DR. PETER MARKS: It looks like it's become a voting question.

MR. MICHAEL KAWCZYNSKI: Well, this is just a poll, not a voting question but just a poll. You asked for it to be a poll.

DR. PETER MARKS: Perfect. Thank you very much.

MR. MICHAEL KAWCZYNSKI: And I will clarify it even in the language up on top that we are just polling

the Committee. Okay.

MS. KATHLEEN HAYES: And Dr. Monto, it looks like everyone was in agreement for this question.

DR. ARNOLD MONTO: Thank you very much as a whole. I will simply report for the record that everybody was in agreement with the poll based on this statement: should healthcare workers or others at high risk for occupational exposure be included in this EUA? Okay. Now, a number of people still have their hands raised. Do all of them continue to wish to make -- give explanations of votes? Starting with Dr. Cohn.

DR. AMANDA COHN: Sure. I think I had my hand raised from previously, but I just want to say that I think this is a really amazing vote for people who are at severe risk for COVID -- older adults as well as people who are at risk in healthcare settings and other high risk settings. And a third dose will protect them, and I just wanted to remind everyone that if you look at when people got vaccinated and how many months out they are that these are the groups that got vaccinated last December and January and February. So

these are the groups that are really beyond six months out and should be boosted in the present time. I am hopeful that FDA and/or VRBPAC come back when there are more data available to evaluate use of this vaccine as a booster dose in younger age groups.

DR. ARNOLD MONTO: Thank you. And I think that's the beauty of an EUA. I think based on past experience it can be changed based on changing data. Dr. Chatterjee?

DR. ARCHANA CHATTERJEE: Thanks, Dr. Monto. I just wanted to echo what -- and I understand, so I'm not going to do that. But I do want to take one moment to actually recognize our colleagues at the FDA and their willingness to work with us on these questions -- on the voting questions. I think this should demonstrate to the public that the members of this committee are independent of the FDA and that in fact we do bring our voices to the table when we are asked to serve on this committee.

ADJOURNMENT

DR. ARNOLD MONTO: Thank you very much, Dr. Chatterjee. A good note to close the meeting. Let me just thank the Committee members and especially Dr. Marion Gruber and Phillip Krause for their longtime service, and I'd like to turn the meeting over to Dr. Atreya to formally close it.

DR. PRABHAKARA ATREYA: Thank you all. Thank you for the wonderful discussions and productive meeting today, and this meeting is formally adjourned. And have a good evening. Thank you all.

[MEETING ADJOURNED]