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Center for Biologics Evaluation and Research (CBER)
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OPEN SESSION

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

ATTENDEES

COMMITTEE MEMBERS	
Arnold Monto, M.D.	University of Michigan
Paula Annunziato, M.D.	Merck
CAPT Amanda Cohn, M.D.	National Center for Immunization 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.	Boston Children's Hospital and Massachusetts Institute of Technology
Patrick Moore, M.D., M.P.H.	University of Pittsburgh Cancer Institute
Michael Nelson, M.D., Ph.D.	UVA Health & UVA School of Medicine
Stanley Perlman, M.D., Ph.D.	University of Iowa
Jay Portnoy, M.D.	Children's Mercy Hospital, Kansas
Eric Rubin, M.D., Ph.D.	Harvard TH Chan School of Public Health, Brigham and Women's Hospital
Mark Sawyer, M.D., F.A.A.P.	University of California San Diego School of Medicine and Rady Children's Hospital San Diego

Melinda Wharton, M.D, M.P.H.	National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention
SPEAKERS AND GUEST SPEAKERS	
Fiona Havers, M.D.	National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention
Matthew Oster, M.D., M.P.H.	Emory University School of Medicine, Children's Healthcare of Atlanta, CDC Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention
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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. I'm Mike Kawczynski, and welcome to the 170th meeting of the Vaccines and Related Biological Products Advisory Committee.

Today, please note that we are having some weather issues with much of our members because this is a broad panel, so there may be periodic changes and pauses just in case any of those have any difficulty staying in the meeting.

But, just like always, I'd like to right away hand it off to my colleague and the chair, Dr. Arnold Monto, so he can take it away.

Dr. Monto, are you ready?

DR. ARNOLD MONTO: Thank you, Mike.

Good morning, everybody. I think we're all at least in the U.S. time zones this time. I'd like to welcome everybody to the 170th meeting, as you've heard, of the Vaccines and Related Biological Products Advisory Committee of the FDA. We're going to be

discussing a very important topic today, on which we are going to have a vote. And we are going to be discussing in open session the Pfizer-BioNTech request for an emergency use authorization for administration of their COVID-19 mRNA vaccine to children 5 to 11 years of age.

As usual, I want to welcome everybody, the participants, including the members and our speakers and everybody online all over, because there's been a lot of interest in this subject. So, welcome to our discussion. And we are going to review the science here and make a decision that I know affects a lot of people.

So, first of all, I'd like to turn the meeting over to our designated federal officer, Prabha Atreya, who is going to go over some of the housekeeping issues, tell you all about how the meeting is going to work, and then introduce the Committee.

Over to 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 Prabha Atreya, and it is my great honor to serve as the designated federal officer -- that is DFO -- for today's 170th Vaccines and Related Biological Products Advisory Committee meeting.

On behalf of the FDA's Center for Biologics Evaluation and Research and the 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 emergency use authorization, EUA, request for administration of their COVID-19 mRNA vaccine to children 5 to 11 years of age.

Today's meeting and this topic were announced in the *Federal Register* notice that was published on October 13th, 2021. I would like to now introduce and acknowledge the excellent contributions of the staff in

my division and the great team that I have in preparing for this meeting.

Can we have the staff slide, please?

Ms. Kathleen Hayes is my co-DFO providing excellent support in all aspects of preparing for this meeting and conducting this meeting as well. Other staff who have contributed significantly are Ms. Monique Hill, Ms. Karen Thomas, Ms. Christina Vert, who also provide excellent administrative support.

I would also like to express our sincere appreciation to Mr. Mike Kawczynski, who is facilitating the meeting today. I also offer kudos to many FDA staff working very hard behind the scenes trying to ensure that today's virtual meeting will also be a successful one like all the previous 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 -- one word -- @fda.hss.gov. The transcriptionists for today's meeting are Ms. Linda Giles and Erica Dunham.

We will begin today's meeting by taking a formal roll call for the Committee members and temporary voting members. When it is your turn, please turn on your camera, unmute your phone, and then state your first and last name. And then, when finished, you can turn your camera off so we can proceed to the next person.

Can we have the member slide, please?

Okay. Let's start today with the chair, Dr. Arnold Monto. Can we start with you, Dr. Monto, please?

DR. ARNOLD MONTO: Yes, Prabha. And, again, we've been doing this for a couple of times recently, and I will introduce myself again. I'm Arnold Monto. I am professor of epidemiology and public health at the University of Michigan School of Public Health.

I've been working for many years on vaccines, on disease occurrence in populations, and particularly respiratory infections, including coronaviruses. And I want to welcome, again, everybody to this meeting. I know there is a great deal of interest.

Back to you, Prabha.

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

DR. PAULA ANNUNZIATO: Good morning. My name is Paula Annunziato, and I lead vaccine global clinical development at Merck. My training is in pediatric infectious diseases, and I'm here today as the non-voting industry representative.

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

CAPT. AMANDA COHN: Good morning. My name is Amanda Cohn. I am a pediatrician at the Centers for Disease Control and Prevention with expertise in vaccine-preventable diseases.

DR. PRABHAKARA ATREYA: Thank you, Dr. Cohn. Dr. Gans?

DR. HAYLEY GANS: Good morning. I am Dr. Hayley Gans. I am professor of pediatrics at Stanford University, and I have trained in pediatric infectious disease. My research focus is on how individuals respond to pathogens. Thank you very much.

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

DR. MICHAEL KURILLA: Thank you, Prabha.

Good morning. Michael Kurilla. I'm the Director of the Division of Clinical Innovation at the National Center for Advancing Translational Sciences within the National Institutes of Health. I'm a pathologist by training with a background in infectious disease and vaccine and other interventional development. Thank you.

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

DR. CODY MEISSNER: Good morning. My name is Cody Meissner. I'm a professor of pediatrics at Tufts University School of Medicine and the Tufts Pediatric Children's Hospital at Tufts Medical Center.

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

DR. PAUL OFFIT: Good morning. I'm Paul Offit. I'm a professor of pediatrics at Children's Hospital of Philadelphia and the Perelman School of

Medicine at the University of Pennsylvania. My expertise is in pediatric infectious disease and vaccines. My specific interest was in coronavirus vaccines. Thank you.

DR. PRABHAKARA ATREYA: Thank you, Dr. Offit. Next, Dr. Pergam.

DR. STEVEN PERGAM: Hello, everyone. I'm Steve Pergam. I am an adult infectious disease physician at Fred Hutchinson Cancer Research Center and the University of Washington Medical Center in Seattle, Washington. And my interest is in infections in immunocompromised patients. Thanks.

DR. PRABHAKARA ATREYA: Thank you. Next, we will introduce our temporary voting members.

Dr. Fuller?

DR. OVETA FULLER: Thank you. Good morning. I am Oveta Fuller. I am an associate professor of microbiology and immunology at the University of Michigan Medical School. I am a virologist scientist, and I work with implementation of science in the community.

DR. PRABHAKARA ATREYA: Thank you. Next, Dr. 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. I'm an immunologist by training, and I do research on pathogenic viruses. Thank you.

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

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

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

DR. OFER LEVY: Good morning. My name is Ofer Levy, and I'm a professor of pediatrics at Harvard --

DR. PRABHAKARA ATREYA: You're breaking up, Dr. Levy.

DR. OFER LEVY: Oh. Can you hear me now?

DR. PRABHAKARA ATREYA: Yes. Thank you.

DR. OFER LEVY: Okay. My name is Dr. Ofer Levy. I'm a professor of pediatrics at Harvard Medical School and director of the Precision Vaccines Program. Our research program applies precision medicine principles to understand age-specific effects of vaccines.

DR. PRABHAKARA ATREYA: Thank you very much. Now, Dr. Patrick Moore.

DR. PATRICK MOORE: Good morning. I'm Pat Moore. I'm at the University of Pittsburgh Hillman Cancer Center. My expertise is in molecular biology and in epidemiology, and my interests are looking at tumor viruses and at epidemics.

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

DR. MICHAEL NELSON: Good morning. Thank you. I'm Mike Nelson, professor of medicine at the University of Virginia and chief of the Asthma, Allergy and Immunology Division there, also president of the American Board of Allergy and Immunology. And my

expertise is in allergic reactions to vaccines and severe adverse events.

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

DR. STANLEY PERLMAN: Good morning. I am Stanley Perlman. I am a professor of microbiology and immunology and a pediatric infectious diseases specialist at the University of Iowa. I have a long-term interest in coronaviruses spanning almost four decades.

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

DR. JAY PORTNOY: Good morning. I'm 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 in Kansas City.

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

MR. MICHAEL KAWCZYNSKI: You're unmuted, Dr. Rubin.

DR. ERIC RUBIN: I don't know if you can hear me, but I can't turn my phone --

DR. PRABHAKARA ATREYA: Yes. Now we can hear you.

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

DR. ERIC RUBIN: Okay. I'm Eric Rubin. You can't see me, but I'm really here. I'm at the Harvard TH Chan School of -- well, there it is -- Harvard TH Chan School of Public Health, the Brigham and Women's Hospital, where I'm an infectious disease physician, and the *New England Journal of Medicine*.

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

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

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

DR. MELINDA WHARTON: Good morning. I'm

Melinda Wharton. I'm an adult infectious disease physician at the Centers for Disease Control and Prevention.

DR. PRABHAKARA ATREYA: Thank you.

Today, we have total 19 participants, with 18 voting members and one non-voting industry representative. Now I will proceed with the reading of the Conflicts of Interest statement for the public record.

The Food and Drug Administration is convening virtually today, October 26th of 2021, the 170th meeting of the Vaccines and Related Biological Products Advisory Committee, VRBPAC, under the authority of the Federal Advisory Committee Act of 1972. Dr. Arnold Monto is serving as the acting chair for today's meeting.

Today, on October 26th, 2021, the Committee will meet in open session to discuss Pfizer-BioNTech's emergency use authorization request for administration of their COVID-19 mRNA vaccine to children 5 to 11 years of age. The topic is determined to be of

particular matter involving specific parties.

With the exception of the industry representative, all standing and temporary voting members of the Vaccines Advisory Committee are appointed special government employees, SGEs, or regular government employees, RGEs, from other agencies and are subjected to federal conflicts of interest laws and regulation.

The following information on the status of this Committee's compliance with federal ethics and conflicts of interest laws, including but not limited to 18 U.S. 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, RGE and SGE consultants of this Committee have been screened for potential conflicts of interest of their own as well as those imputed to them, including those of their spouse or minor children and, for the purpose of 18 U.S. Code 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts and

grants, cooperative research and development agreements, or CRADAs, teaching, speaking, writing, patents and royalties, and their primary employment. These may include interests that are either current or under negotiation. FDA has determined that all members of this Advisory Committee, both regular and temporary members, are in compliance with federal ethics and conflicts of interest laws.

Under 18 U.S. Code 208, Congress has authorized the FDA to grant waivers to special government employees and/or regular government employees who have financial conflicts of interest when it is determined that the agency's need for a special government employee's services outweighs the potential for a conflict of interest created by the financial interest involved or when the interest of a regular government employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Based on today's agenda and all financial interests reported by the Committee members and

consultants, there has been one conflict of interest waiver issued under 18 U.S. Code 208 in connection with this meeting.

We have the following consultants serving as temporary voting members. They are Dr. Fuller, Dr. Hildreth, Dr. Lee, Dr. Levy, Dr. Monto, Dr. Moore, Dr. Nelson, Dr. Perlman, Dr. Portnoy, Dr. Rubin, Dr. Sawyer, and Dr. Wharton. Among these consultants, Dr. James Hildreth, a special government employee, has been issued a waiver for his participation in today's meeting. That waiver was posted on the FDA website for public disclosure.

Dr. Paula Annunziato of Merck will serve as the industry representative at today's meeting. Industry representatives are not appointed as special government employees and will only serve as non-voting members of the Committee. Industry representatives act on behalf of all regulated industry and bring general industry perspective to the Committee. Industry representatives on this Committee are not paid, does not participate in any closed sessions we have, and do

not have the voting privileges.

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

The guest speakers for this meeting are Dr. Matthew Oster, an associate professor of pediatrics at Emory University School of Medicine and a pediatric cardiologist at the Sibley Heart Center at Children's Healthcare of Atlanta -- and he's also a medical officer for CDC COVID-19 response at the Center for Disease Control and Prevention, Atlanta.

Dr. Fiona Havers is a medical officer in the Division of Viral Diseases, National Center for Immunizations and Respiratory Diseases at CDC in Atlanta, Georgia.

Disclosure of conflicts of interest for speakers and guest speakers follow applicable federal laws, regulations, and FDA guidance. FDA encourages

all meeting participants, including open public hearing speakers, to advise the Committee of any financial relationships they may have with any affected firms, its products, and if known, its direct competition.

We would like to remind the standing and temporary members that if the discussions involve any of the products or firms not already on the agenda for which an FDA participant may have a personal or imputed financial interest, the participant needs to inform the DFO and exclude themselves from the discussion, and their exclusion will be noted for the record.

This concludes my reading of the Conflicts of Interest statement for the public record. At this time, I would like to hand over the meeting back to our chair, Dr. Arnold Monto.

Dr. Monto, take it away. Thank you so much.

DR. ARNOLD MONTO: Thank you, Prabha.

First, I would like to introduce Dr. Peter Marks, the Center Director of CBER, who is going to add his welcoming comments to what we've already heard and give us a little bit of the background for the meeting.

Dr. Marks?

FDA INTRODUCTION: WELCOME

DR. PETER MARKS: Thanks very much, Dr. Monto.

Welcome to this 170th meeting of the Vaccines and Related Biologics Advisory Committee. I want to thank the speakers, the sponsor, our open public hearing speakers, our Advisory Committee members, and the FDA staff for their participation today, as well as our virtual audience for joining us.

I'd like to take a moment to provide an overview of today's discussion. We'll be considering the proposed amendment to the emergency use authorization of Pfizer-BioNTech's COVID-19 vaccine for use in children ages 5 to 11 years of age.

Far from being spared from the harm of COVID-19, in the 5- to 11-year-old age range, there have been over 1.9 million infections, over 8,300 hospitalizations, about a third of which have required intensive care unit stays, and over 2,500 cases of

multisystem inflammatory disorder from COVID-19. And there have also been close to a hundred deaths, making it one of the top ten causes of death in this age range during this time. In addition, infections have caused many school closures and disrupted the education and socialization of children.

Following a few introductory presentations, Pfizer will present their data in support of their emergency use authorization amendment, and this will be followed by FDA's presentation, including our benefit-risk assessment. There will then be an open public hearing followed by discussion of the application and a vote on this topic.

Before we get started, I want to acknowledge the fact that there are strong feelings that have clearly been expressed by members of the public both for and against the use of the Pfizer-BioNTech vaccine under emergency use authorization for this age group of 5- to 11-year-old children.

To be clear, today's discussion is going to be about the scientific data that are presented, and it's

not about vaccine mandates, which are left to other entities outside of FDA. I ask that we keep our discourse today civil and focused on the science related to this issue so that we can get through a productive discussion.

Thank you again, and I'll now turn it over back to Dr. Monto.

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

We're going to get into the meat of our discussion right now. First, we're going to hear from FDA about the topic and also the background so that we will learn what we are going to be voting on.

And before I turn over to Dr. Fink, I want to thank FDA for providing us with an agenda which has plenty of time for discussion and to air all of the issues that face us today. Often, we have to compress some of our discussion because of issues of time. That's not the case today. We're going to have a lot of time to discuss these important issues.

Over to you, Dr. Fink.

FDA'S INTRODUCTION OF THE TOPIC PRESENTATION: PFIZER-BIONTECH COVID-19 VACCINE: REQUEST FOR EMERGENCY USE AUTHORIZATION (EUA) AMENDMENT, USE OF A 2-DOSE PRIMARY SERIES IN CHILDREN 5-11 YEARS OF AGE

DR. DORAN FINK: Thank you, Dr. Monto.

Good morning. I'm Doran Fink. I'm the Deputy Director for Clinical Review in the Division of Vaccines and Related Products Applications in the Office of Vaccines at CBER, FDA. I'll be introducing today's topic, Pfizer-BioNTech's request for emergency use authorization of their COVID-19 vaccine for use of a two-dose primary series in children 5 through 11 years of age.

As we all know, the Pfizer-BioNTech COVID vaccine is authorized for use under EUA in individuals 12 years of age and older and additionally is approved under the trade name COMIRNATY for use in individuals 16 years of age and older for active immunization for prevention of COVID-19 caused by the SARS-CoV-2 virus.

Pfizer-BioNTech has now submitted a request

seeking an amendment to their EUA for use of a two-dose primary series in children 5 through 11 years of age. This request includes use of a lower mRNA content -- ten micrograms -- than authorized for use in older age groups, 30 micrograms. That is, we are considering the use of an age-appropriate dose level because, as we pediatricians are fond of saying, children are not simply small adults.

The VRBPAC is convened today to discuss whether available data support that the benefits of the Pfizer-BioNTech COVID-19 vaccine outweigh its risks when administered as a two-dose primary series to children 5 through 11 years of age.

We'll hear a more detailed update on the status of the COVID-19 pandemic from our colleagues from CDC a little bit later this morning.

But just to touch on some high points, more than 45 million COVID-19 cases, including more than 700,000 COVID-19-associated deaths, have been reported to date in the U.S. The Delta variant surge that began during this summer has been associated with increased

SARS-CoV-2 transmission and disease, with the most severe outcomes being predominantly among unvaccinated individuals.

The effectiveness of currently available COVID-19 vaccines has been both demonstrated in clinical trials and further confirmed in real-world observational studies. While the Delta variant surge is now on a downward trajectory, the current number of COVID-19 cases reported daily in the U.S. remains at approximately 70,000.

As we head toward the winter months where people will be forced to go more inside, and as we continue to adhere to a national priority of getting life back to normal as much as possible, which includes keeping children in schools and involved in their activities, it is likely, because we have not reached herd immunity, that transmission of the virus will continue.

Children 5 through 11 years of age have accounted for approximately nine percent of the reported COVID-19 cases in the U.S. overall.

Currently, they account for approximately 40 percent of all pediatric COVID-19 cases. The current case rate in children 5 through 11 years of age is near the highest of any age group.

Clinically significant sequelae of COVID-19, such as long COVID, hospitalizations, and deaths, are less frequent in children than in adults, but nonetheless, these sequelae account for substantial morbidity and mortality in pediatric age groups. Sequelae of particular concern in children include COVID-19-associated myocarditis and multisystem inflammatory syndrome in children, or MIS-C.

So, now, we have in front of us an EUA request for use of a COVID vaccine in children 5 through 11 years of age. I've lost track of the number of times that I've presented this slide, but just as a reminder, here are the statutory criteria for issuance of an EUA.

FDA may issue an EUA of an unapproved medical product following an EUA declaration if the following statutory requirements are met. First, the agent referred to in the EUA declaration can cause a serious

or life-threatening disease or condition. We know this to be the case for SARS-CoV-2. Second, 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, fourth, no adequate, approved, and available alternative to the product is available for diagnosing, preventing, or treating the disease or condition.

The balance of benefits and risks is central to any EUA request and decision, and no more so than in today's discussion.

Benefit/risk considerations and considerations on data to support emergency use authorization of COVID-19 vaccines for use in pediatric age groups were discussed at the June 10th, 2021, VRBPAC meeting. As discussed in that meeting, the benefits of vaccination in pediatric age groups can be assessed via a clinical endpoint efficacy trial that generates data to directly

demonstrate prevention of SARS-CoV-2 infection, or COVID-19 disease.

Alternatively, or in addition, we can rely on established regulatory approach called immunobridging, in which immune response biomarkers elicited by the vaccine in a pediatric age group are compared to those elicited in a reference group, or comparator group, for which clinical endpoint efficacy of the same vaccine was previously demonstrated, for example, younger adults who were enrolled in a clinical endpoint efficacy trial.

In terms of risks, these are assessed in pediatric age groups by safety evaluation in preauthorization clinical trials enrolling participants of that age. Also, these risks are considered in the context of the safety profile and risks described in older age groups.

During the June 2021 VRBPAC meeting, we discussed that the safety database size for pediatric age groups to support an EUA of a COVID-19 vaccine would generally be in the same range as prelicensure

safety databases that have supported approval of other preventive vaccines for infectious diseases, provided, of course, that no safety concerns are identified that could reasonably be evaluated in larger preauthorization clinical trials.

There was some discussion in June about exactly what that size should be, with some VRBPAC members thinking that it should really be toward the upper end of that range. Of course, no matter what the size of the safety database, there will always be uncertainties regarding benefits and risks, including, for example, the risk of vaccine-associated myocarditis or pericarditis. These uncertainties must be addressed through post-authorization safety surveillance and observational studies.

But, going back to today's VRBPAC meeting, as has been mentioned several times, the potential emergency use authorization of COVID-19 vaccines for use in younger children has been a topic of intense anticipation and public debate going back well before we had any age-appropriate data to inform safety or

effectiveness.

But today, data to inform the benefits and risks of the Pfizer-BioNTech COVID vaccine manufactured to provide for an age-appropriate mRNA content are now available for children 5 through 11 years of age. FDA has conducted a comprehensive and independent review of the data, and the input provided by the VRBPAC today will be considered in FDA's assessment of the data and decision regarding regulatory action.

I'd like to close by thanking the VRBPAC for your tireless efforts, critical appraisal of the data, and advice over the many meetings that we've had, in particular over the past month. And I would also like to thank the small army of FDA review staff who has also worked tirelessly, working nights, weekends, and holidays for longer than I can remember, and in particular over the last month literally working around the clock at times to ensure that the information that we present, we are as certain as possible about its accuracy and that we are as transparent as possible in the areas where we have uncertainty.

There are too many FDA staff to put their photos up, but please know that you are appreciated. And I look forward to an objective discussion today. Thank you.

DR. ARNOLD MONTO: Thank you, Dr. Fink. And I want to add my appreciation and that of the Committee to all the work that the FDA staff has done in reviewing the submissions so that we have a fully vetted dossier to work with here as we continue our discussions.

And to continue the background from an FDA standpoint, I'd like now to introduce Dr. Ramachandra Naik, the review committee chair of the Division of Vaccines and Related Products Applications.

Dr. Naik?

FDA'S BACKGROUND PRESENTATION - PFIZER-BIONTECH COVID-19 VACCINE EMERGENCY USE AUTHORIZATION AMENDMENT REQUEST FOR USE IN CHILDREN 5 THROUGH 11 YEARS OF AGE

DR. RAMACHANDRA NAIK: Good morning. I'm Ram

Naik from the Division of Vaccines and Related Products Applications in the Office of Vaccines, and I'm the review committee chair for this EUA amendment. I'm going to provide a brief background for today's Advisory Committee meeting regarding Pfizer-BioNTech's EUA amendment request for the Pfizer-BioNTech COVID-19 vaccine for use in children 5 through 11 years of age.

This is the outline of this background talk. I will briefly describe the currently available COVID-19 vaccines and their uses in different populations, provide overview of the EUA amendment request for use of the Pfizer-BioNTech COVID-19 vaccine in children and the clinical package, briefly describe the Pfizer-BioNTech COVID-19 vaccine formulation requested for EUA, an overview of today's agenda, and finally the voting question to the Committee.

Regarding the currently available COVID-19 vaccines for prevention of COVID-19 caused by SARS-CoV-2, there are three COVID-19 vaccines available under EUA and one licensed vaccine in the U.S.

Pfizer-BioNTech COVID-19 vaccine is authorized

under EUA for use to provide two-dose primary series three weeks apart in individuals 12 years of age and older; third primary series dose at least one month after the second dose in individuals 12 years of age and older who have been determined to have certain kinds of immunocompromise; a single booster dose at least six months after completing a primary series of Pfizer-BioNTech COVID-19 vaccine in individuals 65 years of age and older, 18 through 64 years of age and at high risk of severe COVID-19, 18 through 64 years of age with frequent institutional or occupational exposure to SARS-CoV-2; a single booster dose to eligible individuals who have completed primary vaccination with a different authorized COVID-19 vaccine, also called a heterologous booster or mix-and-match booster.

Each 0.3 mL dose of Pfizer COVID-19 vaccine contains 30 micrograms of mRNA encoding the viral spike glycoprotein of SARS-CoV-2. The licensed vaccine COMIRNATY was approved on August 23rd, 2021, for use in individuals 16 years of age and older. Each 0.3 mL

dose contains 30 micrograms of mRNA, the same amount as that in the Pfizer-BioNTech COVID-19 vaccine.

As currently authorized, COMIRNATY can be used interchangeably with the Pfizer-BioNTech COVID-19 vaccine to provide doses for COVID-19 primary vaccination or a booster dose.

Moderna COVID-19 vaccine is authorized under EUA for use to provide two-dose primary series one month apart in individuals 18 years of age and older, third primary series dose in certain immunocompromised individuals, a single homologous and heterologous booster dose. Please note that the booster dose use population and interval for the Moderna COVID-19 vaccine is the same as for the Pfizer-BioNTech COVID-19 vaccine or COMIRNATY.

The Janssen COVID-19 vaccine is authorized under EUA for use to provide a single-dose primary vaccination in individuals 18 years of age and older, a single booster dose administered at least two months after the primary vaccination to individuals 18 years of age and older, a single heterologous mix-and-match

booster dose.

Topic for today's Advisory Committee meeting, the EUA amendment request for children 5 through 11 years of age. The EUA amendment was submitted on October 6th, 2021. The Pfizer-BioNTech COVID-19 vaccine is proposed to be administered as a primary phase of two doses, 0.5 [sic] mL each, containing 10 micrograms mRNA, three weeks apart in individuals 5 through 11 years of age.

The clinical package includes safety and immunogenicity data. Safety data included are from approximately 1,500 vaccine recipients with two months or more safety follow-up post-dose 2 and from approximately 1,600 vaccine recipients with about two weeks safety follow-up post-dose 2. Breakdown of this subject and details of the data will be provided in the later presentation by FDA and Pfizer.

Regarding the Pfizer-BioNTech COVID-19 vaccine formulation requested for EUA, the formulation of the Pfizer-BioNTech COVID-19 vaccine for which the EUA is being requested is a modified formulation that is

called the Tris/Sucrose formulation. Although the EUA is being requested for the Tris/Sucrose formulation, the vaccine formulation that was used in Study C4591007 in children 5 through 11 years of age was the PBS/Sucrose formulation but diluted to adjust the dosage to ten micrograms.

The Tris/Sucrose formulation uses tris buffers instead of the phosphate-buffered saline, or PBS, used in the previous formulation. Tris and PBS are buffering agents that help maintain the pH and stability of the product.

While PBS/Sucrose formulation of the vaccine indicated for individuals 12 years of age and older uses 0.3 mL dose containing 30 microgram mRNA, the Tris/Sucrose formulation of the vaccine indicated for children 5 to 11 years of age uses 0.2 mL dose containing ten micrograms mRNA.

Pfizer has switched to the Tris/Sucrose formulation because it has an improved stability profile. For example, the Tris/Sucrose formulation of the vaccine can be stored at refrigerator temperature

that is 2 degrees Celsius to 8 degrees Celsius for up to ten weeks. PBS/Sucrose formulation must be stored frozen at minus 80 degrees Celsius until expiry date or minus 20 degrees Celsius for up to two weeks prior to use.

As I stated earlier in Study C4591007 in children 5 to 11 years of age, the PBS/Sucrose formulation was used but diluted to adjust the mRNA content to ten micrograms per dose and 0.2 mL. FDA agreed with Pfizer that an analytical comparability strategy was suitable for evaluation and authorization of the Tris/Sucrose formulation.

In the EUA amendment, Pfizer submitted the required chemistry, manufacturing, and controls data supporting analytical comparability of the Tris/Sucrose formulation to the current PBS/Sucrose formulation. The results of the in-process tests, drug product release tests, product characterization data, and ongoing stability studies were submitted for FDA to review, and manufacturing consistency was established.

This is an overview of today's agenda. After

this FDA introduction, there will be two presentations by CDC. The first one is from Dr. Fiona Havers on epidemiology of COVID-19 in children. Dr. Matthew Oster will present on known safety signals, myocarditis in adolescents and young adults, followed by a five-minute break.

Later, Dr. Bill Gruber from Pfizer will provide the sponsor presentation. After that, there will be three presentations by FDA. Clinical presentations will be provided by Dr. Leslie Ball, followed by Hui-Lee Wong, who is going to present on post-market surveillance of COVID-19 vaccines in the pediatric population in the FDA BEST System. Dr. Hong Yang will present the benefit-risk analysis.

There will be a lunch break for 35 minutes; followed by open public hearing, about 60 minutes; followed by break; and question and answer session later regarding the applicant and FDA presentations; followed by Committee discussion and voting and the adjournment of the meeting.

This is the question to the review Committee:

"Based on the totality of scientific evidence available, do the benefits of the Pfizer-BioNTech COVID-19 vaccine when administered as a two-dose series, ten micrograms each dose, three weeks apart, outweigh its risks for use in children 5 through 11 years of age? Please vote yes or no."

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

Q&A SESSION

DR. ARNOLD MONTO: Thank you, Dr. Naik.

We do have several minutes of time for the Committee to question the FDA representatives about any of the items that they have presented already. We don't want to go into the substance of our discussion yet because we will have plenty of time for that, but mainly the process. So, questions from the Committee, please raise your hands.

Dr. Meissner?

DR. CODY MEISSNER: Thank you, Dr. Naik, for that presentation. And maybe this is a better question

for Pfizer, but why does changing the buffer from phosphate-buffered saline to tris change the stability in such a dramatic way? Do we know?

DR. PETER MARKS: Dr. Meissner, I will let Pfizer respond to that later on. I think I can tell you from my knowledge of chemistry what I believe the answer is, having to do with keeping stability of pH and buffering of solution. But let me defer that to them.

DR. CODY MEISSNER: Thank you.

DR. ARNOLD MONTO: I see no further hands raised, so we are in the unusual position of being a little ahead of schedule. It's my pleasure to introduce the CDC presentations. We're going to be hearing first about the epidemiology of SARS-CoV-2 in children and then some of the issues about myocarditis and other potential side effects of the vaccines and also of SARS-CoV-2 infection.

So, I hand over to Dr. Fiona Havers, who will be telling us about the epidemiology of COVID-19 in children. Dr. Havers?

CDC PRESENTATION: EPIDEMIOLOGY OF COVID-19 IN CHILDREN AGED 5-11 YEARS

DR. FIONA HAVERS: Great. Thank you, Dr. Monto. Appreciate the introduction.

So, my name is Fiona Havers, and I'm a medical officer in the Division of Viral Diseases and also currently on the Epidemiology Task Force in the CDC COVID-19 public health response.

In this presentation, I'm going to give an overview of the epidemiology of COVID-19 in children aged 5 to 11 years, covering incidence and burden estimates, COVID-19-associated hospitalization rates and mortality, multisystem inflammatory syndrome in children, or MIS-C, and post-COVID conditions. I will also talk briefly about transmission and lost in-person learning and other impacts.

As of October 22nd, there have been over 45 million cases of COVID-19 reported in the U.S. The majority of these have been in adults, as have most

hospitalizations and deaths due to COVID-19 illness. However, children have been greatly impacted by the pandemic.

Here are the reported cases by age group, with children 5 to 11 years of age in dark blue. In total, there have been more than 1.9 million cases of COVID-19 reported in this age group. Starting in July and August of this year, there was a sharp increase in cases in this age group.

Over the past two months, we are seeing that children 5 to 11 years, shown here again in dark blue, are making up a greater proportion of total cases, representing 10.6 percent of all cases reported to the CDC the week of October 10th, 2021, while making up 8.7 percent of the population in the 2020 census.

While the data I showed on the previous two slides were on cases reported to the CDC, many infections are asymptomatic or result in mild illness and are not tested and reported. As one way of assessing the full spectrum of disease burden, CDC conducts an ongoing nationwide seroprevalence study

done in collaboration with commercial laboratories. A screenshot of the results on the CDC Data Tracker is shown on the right.

Every two weeks, approximately 50,000 people are tested for SARS-CoV-2 antibodies using de-identified residual sera collected by commercial laboratories. While this is a large-scale study, many jurisdictions have a limited availability of pediatric specimens.

In the age-stratified analysis I will show you on the next slide, this is restricted to 15 jurisdictions that included a hundred or more specimens from children aged 5 to 11 years per two months. We were also limited to a total antibody anti-nucleocapsid assay, which is one that maintains high sensitivity over time and assesses infection-induced antibodies only.

This slide here are the weighted infection-induced seroprevalence estimates from November 20th to June 2021. The estimates are aggregated into two-month time periods to increase precision of the estimates.

In the figure, time is on the X-axis, and seroprevalence is on the Y-axis. Each color represents a different age group.

Children, shown in red, olive, and green, consistently have higher seroprevalence estimates than adults, displayed in blue and purple. The seroprevalence point estimates for ages 5 to 11 are the highest, but the confidence intervals overlap with other pediatric age groups.

For ages 5 to 11, shown in the olive line on the top, the seroprevalence increased from 12 percent in November/December 2020 to 42 percent in May/June 2021. Investigators also used seroprevalence to estimate the cumulative number of infections and compared that with the number of reported cases by age.

Overall, for the general population, the jurisdiction-level infections-to-case ratio had a median of 2.4, with a range of 2.0 to 3.9. For children, the infection-to-case ratio was substantially higher with a median of 6.2 cases for every one infection, with a range of 4.7 to 8.9.

These seroprevalence data suggest that infections in children are less likely to be reported compared with adults, but the children are at least as likely as adults to be infected with SARS-CoV-2. Seroprevalence in children continues to increase with estimated more than 40 percent in children 5 to 11 in May and June 2021. Note that the residual sera assessments collected from children through routine clinical care may not be representative of the general population.

I'm now going to switch and focus on pediatric hospitalization using data from the COVID-19-associated Hospitalization Surveillance Network, or COVID-NET, which is a population-based surveillance system that collects data on laboratory-confirmed COVID-19-associated hospitalizations among children and adults for a network of over 250 acute-care hospitals in 14 states.

Cases are identified in COVID-NET if they test positive for SARS-CoV-2 through a test ordered by a healthcare professional and are hospitalized within 14

days of the positive test. This chart illustrates the weekly rates of COVID-19-associated hospitalizations by pediatric age group, with children aged 5 to 11 years in red.

The cumulative hospitalization rate was 30.1 per 100,000 population for this age group as of October 2nd. As you can see, rates for this age group have been consistently lower than other pediatric age groups. However, note that in September, population-based hospitalization rates were higher in this age group than at any other previous point during the pandemic.

We also do see variations in hospitalizations by race and ethnicity, like American Indian and Alaska Native, Hispanic, and Black non-Hispanic children having cumulative hospitalization rates that were more than three times as high as the hospitalization rates in non-Hispanic white or non-Hispanic Asian children. The disparate impact of the pandemic, including rates of hospitalizations, on these groups is similar to what we have seen in other age groups.

To further put the burden of COVID-19 illness in context, we examined rates of COVID-19 versus influenza-associated hospitalization rates among children ages 5 to 11 years using data from COVID-NET and the Influenza Hospitalization Surveillance Network, or FluSurv-NET.

FluSurv-NET is a long-standing influenza hospitalization surveillance platform that was leveraged to create COVID-NET. It conducts population-based surveillance for influenza-associated hospitalizations from October 1 through April 30th every year. FluSurv-NET has a similar catchment area to that of COVID-NET and uses similar methods for case ascertainment and data extraction.

To compare COVID-19 and influenza-associated hospitalization rates, the COVID-19-associated hospitalization rate was calculated for a one-year period of October 1, 2020, to September 30th, 2021. This annual rate was compared with influenza-associated hospitalization rates from October 1 through April 30th during the 2017/'18 season through the 2020/2021

season.

Influenza-associated hospitalizations occur seasonally with very low influenza detection during most of September, suggesting that few influenza-associated hospitalizations are missed outside the October through April surveillance window. The FluSurv-NET rates from October through April were used to approximate the annual influenza hospitalization rate.

The gray shaded area indicates weeks during which influenza hospitalization surveillance was not conducted. For ease of comparison, influenza-associated hospitalization rates were extended out in a dashed line. The COVID-19-associated hospitalization rates in this age group are shown in yellow, and the influenza-associated hospitalization rates in the three pre-pandemic influenza seasons are shown in red, blue, and green, and the 2020/2021 season is shown in black.

Annual COVID-19-associated hospital rates in children ages 5 to 11 is similar to influenza-associated hospitalization rates for 2017/'18 and the

2018/'19 season, and they were lower than the influenza-associated hospitalization rates for the 2019 and 2020 season.

Notably, influenza hospitalization rates for the 2020/'21 season were exceedingly low. There were only nine hospitalizations being reported across all pediatric age groups for the entire season. During this season, mitigation measures such as school closures and mask-wearing were in place. This suggests that the annual rate of COVID-19 hospitalizations would have been much higher than those for influenza during typical influenza seasons had these mitigation measures not been in place.

I am having a connectivity issue, so I --

MR. MICHAEL KAWCZYNSKI: Yeah, we're bringing you back in right now, Fiona. There you go.

DR. FIONA HAVERS: Great. Thank you. All right. Sorry about that.

MR. MICHAEL KAWCZYNSKI: You should be able to turn your camera back on again.

DR. FIONA HAVERS: All right. There we go.

MR. MICHAEL KAWCZYNSKI: There you go.

DR. FIONA HAVERS: Great. All right. So, going on to the next slide, we also compared outcomes and interventions in children hospitalized with COVID-19 or influenza in the three pre-pandemic influenza seasons.

The median length of stay among children hospitalized with influenza was two days versus three days for children with COVID-19. 21.2 percent of children hospitalized with influenza versus 32 percent of children with COVID-19 required ICU admission. 4.6 percent of children with influenza versus 7.2 percent of children with COVID-19 required invasive mechanical ventilation, and a similar proportion of children ages 5 to 11 with influenza versus COVID-19 died in the hospital at about 0.6 percent.

These data suggest that among hospitalized children, the severity of influenza and COVID-19 in this age group is similar or maybe slightly worse for COVID-19.

These next results are from an investigation

to identify underlying medical conditions associated with increased risk of severe COVID-19 among children aged 5 to 11 who were hospitalized with COVID-19 from March 2020 through August 2021. All children had a primary reason for admission that was related to COVID-19. This investigation identified underlying medical conditions as risk factors for severe disease, defined as requiring ICU admission or invasive mechanical ventilation during hospitalization.

Of 562 children 5 to 11 years, 36 percent had severe disease per this definition, and 0.2 percent died during hospitalization. Approximately two-thirds of the children were Hispanic or non-Hispanic Black. Sixty-eight percent of children had at least one medical condition, with the most common being chronic lung disease, primarily asthma; obesity; neurologic disorders; and cardiovascular disease.

This investigation modeled underlying conditions associated with severe disease among children aged 5 to 11 hospitalized with COVID-19 using multivariable generalized estimating equations.

Estimates are adjusted for sex and race and ethnicity groups and account for geographic clustering of hospitalizations. As shown in the figure, the adjusted relative risk of severe COVID-19 was statistically significantly higher among children with a history of obesity and feeding tube dependence.

As noted previously, during recent months in which the Delta variant has been circulating, there has been an increase in rates of pediatric-associated hospitalizations. However, it was unclear if clinical outcomes were more severe or if the increase in hospitalizations was due to increased community transmission.

This slide here compares outcomes from mid-June through the end of August, a period in which the Delta variant was predominant, to pre-Delta period. Hospital length of stay and proportion admitted to ICU and the proportion requiring vasopressor support or who died during hospitalization were similar in both periods. There was a slightly higher proportion of children who required invasive mechanical ventilation

during the Delta period, but note that the numbers are relatively small, and we're still continuing to monitor these outcomes.

Next, moving to COVID-19 mortality, as of October 22nd, there have been over 730,000 COVID-19 deaths reported in the U.S., the vast majority in adults. However, there have been deaths in children.

Here are the counts of reported COVID-19 deaths by pediatric age. Between January 1st, 2020, and October 16th, 2021, there were 94 COVID-19-associated deaths reported among children 5 to 11 years of age. COVID-19-associated deaths accounted for 1.7 percent of all deaths in this age group. Also note that there is a lag in death reporting, and these numbers may increase.

To put this in context, this table is showing the top-ten causes of death for children 5 to 11 years of age for the year 2019, the most recent year that complete NCHS mortality statistics are available. In the one-year period of October 3rd, 2020, to October 2nd, 2021, there were 66 COVID-19-associated deaths

reported for this age group, which would be equal to the eighth leading cause of death.

I'm now going to move on from mortality to discussing multisystem inflammatory syndrome in children, or MIS-C. This is a severe hyperinflammatory syndrome typically occurring two to six weeks after acute SARS-CoV-2 infection, resulting in a wide range of manifestations and complications. Approximately 60 to 70 percent of patients are admitted to intensive care, and one to two percent die.

There have been 5,217 MIS-C cases reported nationally as of October 4th, 2021. Children aged 5 to 11 is the age group most frequently affected by MIS-C. The median age of cases is 9 years with 39 percent of cases occurring in children 6 to 11 years old. Sixty-one percent of children with MIS-C are Hispanic/Latino or Black non-Hispanic. Adjusted incidence estimates that 100 to 600 cases per million SARS-CoV-2 infections result in MIS-C, varying with race, ethnicity, age, and region.

I'm now going to talk about post-COVID

conditions in children. These encompass a wide range of new, returning, or ongoing health problems, including physical and mental health consequences experienced by patients four or more weeks after initial infections with SARS-CoV-2.

Data on post-COVID conditions are still lacking. However, it does appear that, while less common in an adult, post-COVID conditions do occur in children. In published reports, frequency of their occurrence have varied depending on the characteristics of children studied and other factors.

Further investigation is needed to better characterize post-COVID conditions in children, but a national survey in the U.K. found that seven to eight percent of children with COVID-19 reported continued symptoms 12 or more weeks after their initial diagnosis.

Post-COVID conditions in children appear after both mild and severe infections and after MIS-C. Symptoms are similar to those seen in adults and include fatigue, cough, muscle and joint pain,

headache, insomnia, and trouble concentrating. It's important also to consider the impact of post-COVID conditions on quality of life, which include limitations of physical activity, feeling distressed about symptoms, mental health challenges, and decreased school attendance and participation.

I'm now going to switch gears and talk briefly about children and transmission of SARS-CoV-2. Multiple factors impact the transmission of SARS-CoV-2 virus. They include the presence and type of symptoms of the index case, type and timing of exposure, viral load, and variant.

Some studies have observed similar secondary infection rates between children and adults, and others have found lower infection rates among children compared with adults, although some of those are earlier studies that likely underestimated infections in children.

However, what is clear is that secondary transmission from children both to other children and to adults can and does occur, with data from household

and school settings. Multiple household studies, outbreak, and contract-tracing investigations have demonstrated efficient transmission among children and adults in multiple settings.

Here is a recent MMWR describing transmission of the Delta variant within a classroom setting in an elementary school with an attack rate of 50 percent among students too young to be vaccinated. You can see from the figure on the right that some students, in blue, were links in transmission to other students, siblings, and their parents.

In addition to the severe outcomes of hospitalization, ICU admission, and death and the potential for MIS-C and post-COVID conditions, there are many other adverse outcomes on children from the pandemic, including worsening emotional and mental health, decreased physical activity, and loss of caregivers.

Lost in-person learning is another potential outcome of COVID-19 illness and exposure among children. I'm not going to talk about this or other

adverse outcomes at length. However, numerous reports have described the negative impact of lost in-person learning on social, emotional, and physical health of children, with disproportionate impacts on children of color.

We are showing data from the School Dismissal Monitoring System, which performs daily systematic searches of Google, Google News, and Google Alerts to assess information on unplanned school disclosures [sic], including the number of districts, individual schools, and students and teachers impacted.

In this school year to date, more than 2,000 schools had unplanned closures, impacting more than a million students. You can see from the map on the right the range of school closures by state.

In summary, children ages 5 to 11 are at least as likely to be infected with SARS-CoV-2 as adults. There have been more than 1.9 million reported cases and seroprevalence estimates of more than 40 percent in May and June 2021. Seroprevalence data is consistent with the realization that younger children are less

likely to be recognized and tested and reported as cases than adults.

Children 5 to 11 years of age are at risk for severe illness from COVID-19. There have been more than 8,300 hospitalizations to date, the hospitalization rates three times as high for non-Hispanic Black, non-Hispanic American Indian and Alaska Native, and Hispanic children as for non-Hispanic white children.

Cumulative hospitalization rates are similar to pre-pandemic influenza-associated hospitalization rates despite the mitigation measures put in place during the pandemic. Severity is comparable among children hospitalized with influenza and COVID-19, and approximately a third of the children ages 5 to 11 who are hospitalized require ICU admission.

In addition, MIS-C, a serious complication, is most frequently seen among children ages 5 to 11 years, and post-COVID conditions have been seen in children in this age group. Secondary transmission from young school-aged children can and does occur in both

household and school settings. And COVID-19 in children leads to lost in-person learning and other adverse outcomes.

There have been a lot of people involved in the research included in this presentation and in the development of this talk, and I'd like to thank all of them. And now I am happy to take questions. Thank you very much.

Q&A SESSION

DR. ARNOLD MONTO: Thank you, Dr. Havers. We now have some time for questions. And we want to be able to examine the epidemiology and impact of this SARS-CoV-2 in the age group in question, so please raise your hands.

I see Dr. Kurilla.

DR. MICHAEL KURILLA: Thank you, Arnold.

Thanks for that presentation, Fiona. Two questions, one related to MIS-C. My impression is that the median age is somewhere around 12 or 13 for MIS-C?

DR. FIONA HAVERS: I believe it's around 9 was what I -- I think it's around 9. And we do see it in older children as well.

DR. MICHAEL KURILLA: Okay. What I'm trying to get a sense of, is there any evidence in the 12 crowd and older as to whether or not vaccination has in fact impacted MIS-C? That's my first question.

My second question is -- and I'll just say both at the same -- is, with regard to hospitalizations, there's been some reports that being hospitalized with COVID versus hospitalized for COVID -- that hospitalized with COVID may be on the order of 40 to 45 percent for kids.

Is your hospitalizations -- do you distinguish that, or any child in the hospital for any reason, if they have a positive COVID test, then they are a COVID hospitalization?

DR. FIONA HAVERS: That's a great question. So, I do want to clarify that the median age for MIS-C is 9, but we do see it in older children. I don't know yet that we have seen the impact on -- there is a lag

in MIS-C reporting, and so I'm not sure that we would necessarily tease out if there has been a decrease in rates of MIS-C in older children who are eligible for vaccine and adolescents. We have seen it slightly decrease in proportion of hospitalizations for children ages 12 to 17 relative to what they had been before when you compare it to other pediatric age groups.

Coming to your second question regarding the proportion of children that are hospitalized, in COVID-NET, we do have the ability to see kind of what their primary reason for admission was. For the rate population, we include all children that have a positive SARS-CoV-2 regardless of the reason for admission.

But, when we're doing further analyses like the ones where I presented with underlying conditions and the outcomes, we remove the children that were admitted for other reasons. And those are primarily things like -- in this age group, in the 5- to 11-year-olds, it was like planned surgeries, trauma, psychiatric admissions requiring medical care.

In this age group, in 5- to 11-year-olds, we had about, I think, 19 percent of children who were admitted with a positive SARS-CoV-2 test were probably admitted primarily for other reasons. It's not always totally clear cut, and sometimes the reason for admission then develops into a more COVID-19 illness-related admission. But we thought it was about 20 percent.

But, in terms of the outcomes, the 36 percent that I presented that ended up in the ICU in this age group, those were all just among children who were primarily admitted for COVID-related illness.

DR. MICHAEL KURILLA: Okay. And then, last question, what percentage of the deaths in this age group is MIS-C related?

DR. FIONA HAVERS: That's a great question, actually. These deaths are reported through two different systems. And of the deaths that I noted there in this age group, about 23 of them -- or about 20 or so; we actually looked up these numbers yesterday to see what the overlap was -- about 20 of them were

related to MIS-C. However, there have been 44 deaths total for MIS-C that have been reported in children under 18. So, that's actually among all children.

So, I think a proportion of them, but there's two slightly different reporting systems, and there is a lag for both death-reporting for COVID-associated deaths and then for MIS-C deaths, which are reported separately. So, the numbers that I included for the 5-to-11 age group does include some MIS-C deaths but not all of them.

DR. MICHAEL KURILLA: All right. Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Hildreth?

DR. JAMES HILDRETH: Thank you, Dr. Monto. Thank you, Dr. Havers, for your very informative presentation.

I just want to clarify a couple of things that you referenced in your talk: that if I understand it, the prevalence of COVID-19 among -- or at least infection by SARS-CoV-2 among children this age is 42 percent as of early summer. Is that correct?

DR. FIONA HAVERS: That was what we were

seeing in the seroprevalence studies, yes.

DR. JAMES HILDRETH: And do you have any data as to whether or not that prevalence is uniform across the racial groups? Is it higher in some than others?

DR. FIONA HAVERS: The residual clinical sera that's used in these studies I don't think has complete race and ethnicity data, so I don't think that we would know that. I do think that we know from other studies and also from the studies that have data on hospitalizations that the incidence, as I mentioned, among non-Hispanic Black and Hispanic and AI/AN children is much higher in terms of hospitalization.

So, I imagine that we've seen a greater impact on communities of color in general, so I would imagine the prevalence is probably likely higher in children of color, as well, for seroprevalence.

DR. JAMES HILDRETH: Okay. Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Levy?

DR. OFER LEVY: Thank you, Dr. Havers, for an excellent presentation.

I wanted to ask a few questions regarding

obesity. Clearly, obesity has been well established as a risk factor for severe COVID in adults. Obesity rates have been increasing among children in the United States. You highlighted in your presentation some analyses that suggested obesity is also a risk factor for severe COVID in children.

As you know, many factors impact obesity, including regional factors, racial/ethnic factors, and others. And I'm just wondering -- it went by a little quickly -- what kind of adjustments did you make to make sure that wasn't confounded in the pediatric case? How well can we hang our hat on obesity in children, in 5- to 11-year-olds, as a risk factor here? Thank you.

DR. FIONA HAVERS: No, thank you for that. The multivariable model that I showed adjusted for age. It also adjusted for geographic clustering of hospitalizations within the COVID-NET system, and we also adjusted for race and ethnicity as well as other underlying medical conditions. And we have very complete race and ethnicity data within that system.

So, I think that -- I mean, there's obviously

a lot of factors that go into it, but I think that it did seem to be an independent risk factor. Those were only among children that were already hospitalized for COVID-19 illness, and so I think that you should keep that in mind when looking at the data. But that was among severe outcomes among already-hospitalized children.

DR. OFER LEVY: But you do believe that's an independent risk factor, then, for severe outcomes?

DR. FIONA HAVERS: I think so, yes.

DR. OFER LEVY: Yeah. Thank you.

DR. FIONA HAVERS: Yeah.

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

DR. HAYLEY GANS: Thank you, Dr. Havers. I really appreciate the information you provided to us today.

I had a couple of questions about long-term effects because I think those are very important. And I realize this is a new virus; we haven't had it for that long. But there's been at least a year for some of the studies, particularly relating to some of the

long-term outcomes with MIS-C.

And I'm particularly interested in some of the data that is looking at the cardiac effects of long term, particularly because we know that this virus has receptors on the heart, and so even less symptomatic disease could lead to scarring and electrical abnormalities. So I'm particularly interested in breaking that down a little further.

And I know we're going to have a talk on myocarditis/pericardi- -- I don't know if that's going to be covered there. But since you talked about MIS-C, there are some studies looking particularly long term (audio skip) wondered if you had any further breakdown of the data.

And then, related to Dr. Hildreth's, the long-term outcomes in children, since there does seem to be health disparities in illness and hospitalizations, have people looked at the long-term outcomes (audio skip) in those, (audio skip) well, to see (audio skip) they're at higher risk for some of the adverse (audio skip)?

DR. ARNOLD MONTO: And, as we discuss this, Dr. Havers, I'm being reminded we're going to be hearing about this again in the next presentation. Please go ahead.

DR. FIONA HAVERS: Yeah. I'm going to defer all of the questions about myocarditis to Dr. Oster, who's a pediatric cardiologist and I think will probably have the best data available on that question.

In terms of the long-term outcomes, I don't know that this is as well studied as we would like yet. I mean, I think there are studies going on that are looking at long-term outcomes in different groups, but I don't necessarily think -- we don't have a lot of good data or very concrete data on that yet. But I definitely think it has been a very active research area.

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

DR. STANLEY PERLMAN: Yes. So, this is actually a continuation of the questions that were just asked because one of the things in thinking about the cost-benefit ratio of this vaccine is its effects on

long-term disabilities. And it sounds like a lot of what we're hearing is that these children are developing something that looks like chronic fatigue syndrome or some version of that.

And do we have any idea, is this behaving like chronic fatigue and not disappearing, or is it going away after a few months? Do you have any information about the duration of how long those symptoms last?

DR. FIONA HAVERS: I think that it does go away in some children, but I think that this research is still ongoing. I don't have great answers to that right now. I mean, I think that the studies that have come out have shown that there has been some fairly durable symptoms and that people several months out of their infection are still having symptoms.

But I think, in terms of much longer effects, we don't have a lot of great data in the pediatric age population. And then Dr. Oster, I think, is going to be also talking about some of the longer-term cardiac side effects of MIS-C in his presentation as well. So, he may have some more information to share there.

DR. STANLEY PERLMAN: Okay. Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Wharton?

DR. MELINDA WHARTON: Fiona, great presentation. Do we know anything about the frequency of reinfection or second infections in children?

DR. FIONA HAVERS: The question of reinfection and second infection is definitely an area of active interest. I think that we don't have great data on that at this point. I do think that we are seeing more and more second infections just in the population in general, but I don't have any data on this right now.

DR. ARNOLD MONTO: Dr. Portnoy?

DR. JAY PORTNOY: Thank you, Dr. Havers, for that presentation. It obviously took a lot of effort to accumulate all of that information. I have two quick questions. First one is about the seroprevalence surveillance that you're doing. Do you have the ability to separate recent infections from infections that happened a long time ago, perhaps by looking at IgM and IgG antibody types?

DR. FIONA HAVERS: For the data that I

presented here, I think that they don't have a sense of the timing of infection. Also note that of the residual sera specimens that they have, they exclude people that have sort of an ICD-10 code or something that indicates that they were being evaluated for a recent SARS-CoV-2 infection.

So we don't have good information on the timing of it. I mean, I do think that the change in time in seroprevalence does sort of give some idea kind of on a general population level, but we don't have good individual-level data on symptoms that go in with the seroprevalence studies.

DR. JAY PORTNOY: And given the fact that there's likely to be an underestimate of the prevalence of COVID-19 in young children because many of them are asymptomatic, how do you adjust for the hospitalization rate given the fact that you're likely underestimating the total number of people who have the disease?

DR. FIONA HAVERS: Well, I think for hospitalizations, it's a little bit different. I think, generally speaking, you're totally right. I

think that cases and infections are definitely underestimated in kids because they are not being tested, and many of them are asymptomatic or have mild illness or don't seek medical care.

For hospitalizations, I think many of the children, when they're being admitted and meet the bar for hospitalization, they generally are being tested for SARS-CoV-2. And so, for the COVID-NET data that we presented, those are all based on clinician-driven testing. And so, a child did have to have -- it wasn't surveillance testing. A child had a clinician order a SARS-CoV-2 test.

So, it is possible that we are underestimating, a little bit, the hospitalization rates. But I think, generally speaking, for hospitalizations, we feel pretty good that we have good case ascertainment within COVID-NET and that we're not missing a lot of pediatric hospitalization cases with more serious illness.

DR. JAY PORTNOY: But when you express it in terms of --

DR. ARNOLD MONTO: Thank you. We're --

DR. JAY PORTNOY: Okay.

DR. ARNOLD MONTO: -- going to have to move on. We have more hands, and we're going to be having lots more time for discussion.

Dr. Moore?

DR. PATRICK MOORE: Thank you. That was a really nice presentation. It really helped a lot. Do you have any data from COVID-NET or other places that tells us more about whether there's vaccine efficacy or effective vaccines on, for instance, nucleocapsid antibodies through a conversion, particularly among 12- to 18-year-olds, getting at does the vaccine look like it's inhibiting transmission, particularly asymptomatic transmission, which is so critical to this epidemic?

DR. FIONA HAVERS: I am not aware of data, particularly in the adolescent age group, that shows that in terms of its impact on seroprevalence. We don't have that in COVID-NET. I can certainly check with my CDC colleagues and perhaps get back to you on that later today.

DR. PATRICK MOORE: It's such a (audio skip) question.

DR. FIONA HAVERS: Yeah.

DR. ARNOLD MONTO: Thank you. One more question because we're going to be circling back again in a more general discussion after the next presentation.

Dr. Sawyer, final question.

DR. MARK SAWYER: Thanks, Arnold.

So, we just discussed that a fair number of children will have been infected and not tested and recognized at the time. In the 12- to 16-year-old age group, do we have information about receipt of vaccine in close proximity to prior infection and what that does to the safety profile of the vaccine? Because inevitably, as we start rolling out this vaccine in younger kids, we're giving it to some children who may have been recently infected. And I'm wondering if you have that data, or are we going to get to that point sometime today?

DR. FIONA HAVERS: That's a great question.

I'm going to defer vaccine safety questions to Dr. Oster and his presentation, and I think he'll be in a better position to answer that than I will because I think you're certainly going to address, potentially, vaccination close to the time of natural infection. So, (audio skip) question to him.

DR. ARNOLD MONTO: Thank you. That's a nice segue into the next presentation, "Known safety signals (Myocarditis in adolescents and young children)," Dr. Matthew Oster. He's from the Center of Disease Control COVID Response. He's also a pediatric cardiologist at Sibley Heart Center, the Children's Healthcare of Atlanta, Emory University.

Dr. Oster?

CDC PRESENTATION: mRNA COVID-29 VACCINE-ASSOCIATED MYOCARDITIS

DR. MATTHEW OSTER: Great. Thank you very much for having me. The usual CDC disclosures.

Today, I was asked to talk about three areas,

really, as it pertains to myocarditis, but first to give a brief update on cases of myocarditis after COVID-19 vaccine -- and some of this will be information you may have seen previously -- but then talking a little bit more about the different types of myocarditis that we have seen, especially in the COVID era, and then what do we know so far about outcomes following myocarditis?

So, first, I'd like to present some information from the Vaccine Adverse Event Reporting System, or VAERS. This graph shows the estimates of reports of myocarditis among males. This is per one million doses administered with a seven-day risk period with an estimated background incidence rate of about 0.2 to 1.9 per million.

The shaded areas shown show a reporting rate that exceeded the background incidence. As you can see, for those receiving Pfizer, following dose 1, it exceeded background for ages 12 to 24, and then for dose 2 for ages 12 to 49 with peaks in adolescents.

For Moderna, similarly, there was an excess

risk noted after dose 1 in young adults, as well in dose 2 in young adults from 18 to up to 49 with the peak again in the 18-to-24 age range.

For females, the rates were much lower, although there were some areas where there was an excess risk. This was following dose 2 primarily, both for Pfizer in females ages 12 to 24 and for Moderna in females ages 18 to 29.

Before the VAERS reports, I wanted to touch a moment on what we know about those less than 29 years of age. CDC has been reaching out to reporters to find more information and to investigate these cases. Of about 1,600 total preliminary reports, 877 were able to be adjudicated as meeting case definition.

There was a small number that were able to be determined not meeting case definition per myocarditis. There are 637 that are still under review, meaning there was not enough information given at the time of the VAERS reports to truly confirm the case, but investigations are ongoing to gather more information.

Of those meeting case definition, 829 were

hospitalized, and, at the time of their report, 789 had been discharged with 77 percent of those reported to have recovered from their presenting symptoms at the time of the report. Thirty-four were not hospitalized and were seen in outpatient settings.

This is data from Vaccine Safety Datalink, an ongoing project to evaluate health records from a number of different health systems to look for active signals of safety risks following vaccine administration. Vaccine Safety Datalink, I'm going to present the data for just the adolescents here, ages 12 to 17 years. This is only those receiving Pfizer-BioNTech. And they looked at not only a 0- to 7-day interval but also a 0- to 21-day interval.

But, as you can see, the primary events were in the zero- to seven-day interval, similar to what was seen in VAERS, with no events in the comparison interval. Thus, rate ratios were not able to be computed, but, as you can see, the risk was high.

They also reported excess cases per risk period per one million doses, with the highest being

after dose 2 with an estimate in the zero-to-seven group about 54. And those numbers are very similar to what was seen in the VAERS data.

But now I'd like to speak a little bit, though, about the different types of myocarditis. Myocarditis, put simply, is inflammation of the myocardium, or heart muscle. But when we talk about myocarditis, there can be different etiologies, presentations, and outcomes.

So, classic myocarditis, for lack of a better term -- when I say that, I'm going to be speaking about myocarditis in the pre-COVID-19 era. But, since the onset of the pandemic, we have noticed some other types of myocarditis, namely COVID-19-related myocarditis, that is, acute COVID-19 infection leading to myocardium inflammation. MIS-C myocarditis, which you heard a little bit in the earlier presentation, I'm going to expand upon. And then COVID-19 vaccine-related myocarditis is one of our very concerning adverse events.

So, first, our classic or pre-COVID

myocarditis is thought to have a number of different etiologies. Most are thought to be due infectious when a cause is found, but often, a cause is not necessarily identified. We'll call that idiopathic myocarditis.

But there can be a number of non-infectious etiologies as well, and these types of myocarditis are still around in our background, right? So, we need to remember to be checking for these and to be conscious of those in patients.

This slide shows the epidemiology of myocarditis in pre-COVID era with children on the left and adults on the right. And you'll notice a couple of things here. In children, there was a peak kind of in the first year of life, and many of these cases are thought to have a genetic component. And then, at least among children, it starts to peak around adolescence.

In adults, again, peaks start in adolescence and young adulthood and then slowly comes down over time, particularly for males. Females seem to have a more constant rate over time with maybe a slight uptick

in the 50s.

So, two things to note about these graphs. So, first, at least for the 12-and-older range, these patterns seem very similar to what we were seeing for the vaccine-related myocarditis. And I think these are different entities, but it is interesting that the epidemiology in terms of incidence and some of the sex distribution seem to have a very similar pattern.

And then, second, I know we're talking about children 5 to 11 years today. If that pattern holds, then we would expect that the rates of myocarditis in the 5- to 11-year-old group, even if they were given the same dose in the lower group, would be less. But, again, this is comparing two diseases which may not be exactly similar.

The pre-COVID-era myocarditis in children can have a very severe outcome, especially in the younger children. But overall mortality is about four to seven percent, with heart transplant four to nine percent of cases.

What about MIS-C myocarditis, or myocarditis-

associated multisystem inflammatory syndrome? In data reported to CDC from states on case report forms, myocarditis was indicated as occurring in 17 percent of cases. In early reports from COVID-NET, cardiovascular involvement overall was quite common, about 80 percent of children having some sort of cardiovascular involvement, with elevated troponin in about 50 percent. Those cases would -- combination of elevated troponin and symptoms would be case definition for myocarditis as per the CDC definition.

And what about myocarditis due to COVID-19? In this MMWR, we looked at the association between COVID-19 and myocarditis, and this is using hospital administrative data from March of 2020 through January of 2021. As you'll see here, one of the highest areas for risk, at least for myocarditis due to COVID, was in the less-than-16-year age group.

However, it is unclear in looking just at this data how much of that myocarditis was due to acute COVID infections versus how much was due to cases of MIS-C. Prior to January 2021, there was not a specific

ICD-10 code for MIS-C, and so, many cases had COVID classified as part of their disease illness.

This is data from two large administrative -- and some other -- health records data sets. This is very preliminary data that these entities shared with us.

So, first, using EPIC data -- this is including over about 700 hospitals with primarily inpatient. There are some outpatients in here. But in looking at cases of COVID-19 without MIS-C -- there was no codes for MIS-C; this is since January this year -- myocarditis was diagnosed in 0.02 percent. But in MIS-C, myocarditis was diagnosed in about eight percent. So, most of the myocarditis seems to be due to MIS-C.

Looking at data from Children's Hospital Association with their Pediatric Hospital Information System, we see a similar trend where the acute cases of COVID-19 -- this is only inpatient admission from their data -- myocarditis was diagnosed in 0.08 percent of COVID-19 admission but nine percent of MIS-C admissions, with MIS-C myocarditis outnumbering the

COVID-19 myocarditis in both base systems.

So, it appears that a lot of the myocarditis, at least associated with COVID, in kids seems to be due to MIS-C, although there are certainly some cases due to COVID-19, but it was much rarer.

Now I'd like to present some early data from a paper published on medRxiv. This is actually a report from my role at Children's Healthcare of Atlanta, where I supervised one of our cardiology fellows to look at what was our single-center experience with the different types of myocarditis. We did not include acute COVID-19 myocarditis because we really hardly had any cases.

So, this graph, it seems busy, but I'm going to show you just a highlight here, though, is that for a number of different laboratory measures -- which are troponin, B natriuretic peptide, lymphocytes, white blood cells, C-reactive protein, and platelets -- the classic myocarditis, which is the leftmost group in each panel, and the vaccine-related myocarditis, which is the rightmost group in each panel, seem quite

similar in their presentation. And the MIS-C group in the middle is very different, at least in their presentation.

This makes us think that, again, not all these types of myocarditis are the same. When we looked at acute outcomes -- and so, for this one, we looked primarily at ejection fraction echocardiogram -- there were no deaths in any of these groups. So, first, let's look at the blue and the red groups.

So, the blue is the classic or pre-COVID-19 myocarditis group, and the red is the MIS-C myocarditis group. Both of these groups, on presentation, at least, had a fair number of patients, so about two-thirds of their patients, who had decreased ejection fraction by echocardiogram.

But as you'll see, whereas previously the classic myocarditis group, by about 10 to 15 days, about 30 percent of children still had decreased ejection fraction, by that same period in the MIS-C group, nearly all had returned to normal ejection fraction, so normal function by their echocardiogram.

In the vaccine-related myocarditis group -- and this is just in our first nine patients -- decreased function, decreased ejection fraction, was rare, in about two of the nine patients. It was not nearly as common. And those patients had full resolution back to normal function within a few days.

Now let's move to some of the longer-term outcomes. So, what do we know about the pre-COVID era for outcomes? First, we know that myocarditis portends a risk of sudden death in children and adolescents. In a paper published last year, it was noted that five to ten percent of sudden death in adolescents and young adults was attributable to myocarditis.

And I want to make clear that's not saying that five to ten percent of those with myocarditis are at risk for sudden death. It's saying that five to ten percent of sudden death on autopsies were found to have myocarditis, usually not previously diagnosed. And it is findings like this that help inform the latest guidelines in the American Heart Association/American College of Cardiology.

These were published in 2015, and their approach to myocarditis is that children, before returning to competitive sports for children and adults, should basically have a full cardiac evaluation to look for any evidence of decreased function, myocardial information, or arrhythmias.

Many kids have abnormalities on their MRI in myocarditis. I didn't show it here, but in the VAERS reports, about 72 percent who had an MRI had some inflammation or other findings consistent with myocarditis on their MRI. But it's unclear whether resolution of late gadolinium enhancement -- and you'll see that come up later -- should be required in MRI. This is still under research and trying to figure out the meaning of this.

But the important thing to note, also, is that this recommendation from American Heart Association/American College of Cardiology specifically mentioned that it is independent of age, gender, and left ventricular function. So having normal function does not necessarily mean that you're out of the woods

from a risk standpoint.

So, what are risk factors, though, for myocarditis outcomes? Again, in the pre-COVID era -- and this paper was recently published, which had a good summary of factors and variables that can lead to a good outcome or poor outcome.

So, as it relates to vaccine-associated myocarditis, I put in a box some of their features, which are very similar or might portend a good outcome. So, first, chest pain and Class New York Heart Association I and II, this is a very common presentation of vaccine-associated myocarditis. They're not presenting, typically, with some of the other features that you'd see that portend a bad outcome.

Electrocardiogram -- many of the vaccine-associated myocarditis cases have ST elevation with myocarditis, but other findings are rare. Troponin -- early rise and fast decline associated with a good outcome, and that is the typical story that we see with vaccine-associated myocarditis, although occasionally

there can be some persistent abnormal levels.

And then echocardiogram, preserved LV ejection fraction at onset or early improvement of that, that seems to be the typical finding with vaccine-associated myocarditis.

And, again, here we'll see cardiac magnetic resonance imaging. This is the area that we need to follow and see in these kids because presence of late gadolinium enhancement or persistence of this over time can be associated with a poor outcome. And, as I mentioned, on presentation, a fair number of those with vaccine-associated myocarditis did have some of these findings despite having all the other factors associated with a good outcome.

What are some of the long-term outcomes of pre-COVID myocarditis? This is a paper from 2004, so it is from a couple of decades ago, looking at myocarditis in children. And they broke these up into three groups and looked at them over about 14 years. Top group is the acute myocarditis group. Second is borderline myocarditis, and third is groups of dilated

cardiomyopathy that wasn't inflammatory, so not really an acute myocarditis picture.

And it showed that those in acute myocarditis actually did quite well over time. So, once you get over the acute phase, the long-term outcomes tended to be quite good in children. In adults, the picture is a little bit different. Again, this is an older study, from 1995.

This study was comparing immunosuppressive therapy for myocarditis and showed no difference in long-term outcomes. But the long-term outcomes in this group -- and in total, there were 111 patients with a mean age of 42 years -- at about five years, cumulative mortality is about 50 percent.

What do we know about the three- to six-month outcomes for multisystem inflammatory syndrome in children? This question came up earlier. So, this is looking first just at ejection fraction, so the cardiac function, the red line being normal ejection fraction. And, as you can see in that first blue box, a number of kids had an abnormal ejection fraction on presentation

or during their lowest EF during their course of their illness.

But, by discharge, most have reached normal ejection fraction, and by two weeks, almost all had normal, with then all having normal at six months. And this was in 50 children of a median age of about 8.5 years.

What about the cardiac magnetic resonance imaging? So, this is in about 19 kids, and this group did follow-up MRIs, and they found no persistent cardiac changes in cardiac MR at follow-up. There have been some other reports here, some smaller changes, but it is quite rare in kids.

Not shown here, because I was asked to speak primarily on myocarditis, but this question did come up -- concerns about other factors. There was a paper published in the U.K. looking at some six-month outcomes for kids with MIS. They had similar findings from some of the cardiac findings, but they also looked at some quality-of-life questions.

I will point out about 20 to 30 percent of

children and their parents reported either mild or severe impairment on at least one scale with the highest being an emotional scale, having some difficulties with the emotional level. There was no control group, so it's hard to determine how much of that was due to just the COVID pandemic setting versus their own personal illness. But it is interesting to continue to follow.

What do we know about COVID-19 vaccine-associated myocarditis in adolescence? We don't know a whole lot yet. This paper, looking at 54 patients, a mean of 15 years, again 92 percent male -- this was looking really at about one month since vaccination for a mean of 35 days. About 13 percent still had persistent symptoms despite all of them having normal echocardiograms. Eighty percent had normal EKGs, but about 20 percent obviously still had some abnormality.

Troponin, when it was checked, was usually normal, although a few had borderline findings. And only two had had MRI by this time, at about two months and two and a half months -- did show improvement in

myocardial edema but some persistence of late gadolinium enhancement.

Vaccine Safety Datalink is also following up the cases that have been identified. They're doing chart review to look at their follow-up. As of earlier this month, they had done reviews of 47 cases, and 37 of whom had had at least one follow-up visit. And, of those, some of them had had a follow-up visit at least three months since their initial encounter.

And I'll point out down this slide, any new or worsening symptoms, present down about 20 to 50 percent. And this did vary by age. Troponin levels, EKG, and echocar- -- often had some abnormalities, again in about 20, 50 percent. Echocardiograms were typically normal when they were performed. Only one MRI had been completed in this group to date.

I classified these groups as their current status, and these are not mutually exclusive groups. But, by age, about 30 percent of those 12 to 17 have been given a status of recovered, meaning no medications, no exercise restrictions, no ongoing

symptoms, and about 50 percent of those in the 18- to 39-year age.

CDC is also doing an investigation to investigate the long-term effects of myocarditis, and CDC is reaching out to patients who have been identified in VAERS case reports. And the purpose is to assess their functional status and clinical outcomes long term.

There's a two-part component to the survey: first, contacting the patients themselves or their parents to assess functional status, clinical symptoms, quality of life, and other ongoing clinical needs; and to ask them to identify a healthcare provider that they're seeing, which is usually a cardiologist, to try to gather information on their cardiac health and functional status.

So, to date, about 680 patients have reached the 90-days-post-myocarditis diagnosis. About 41 percent of these have received one phone call. About 60 percent of those have completed the survey, and about 168 patients were able to identify -- 132 of them

were able to identify a cardiologist or healthcare provider. About 26 of them had completed the survey. So, more data on this will be forthcoming.

In summary, myocarditis is a rare but important adverse event following COVID-19 vaccination, and not all myocarditis is the same. There may be some similarities in presentation with some or in acute outcomes with others, so it's hard to do straight comparisons. So, that's sometimes just the best that we have.

And we really need to see what the long-term outcomes for these kids will be. So far, the data for follow-up results is sparse, but ongoing follow-up is in progress.

Thank you very much, and I'd specifically like to thank Tom Shimabukuro, John Su from the Vaccine Task Force, and Niki Klein from Vaccine Safety Datalink for sharing some slides, Sam Butler from EPIC, and Matt Hall and Cary Thurm from the Children's Hospital Association, for sharing some very preliminary data.

Thank you. I'm happy to take any questions.

Q&A SESSION

MR. MICHAEL KAWCZYNSKI: Arnold looks like he's reconnecting his audio here momentarily, so we'll just give him a moment. There we are.

Arnold, are you back?

DR. ARNOLD MONTO: Am I on?

MR. MICHAEL KAWCZYNSKI: Yes, you are, sir. Take it away.

DR. ARNOLD MONTO: Okay. Somebody sent me a FaceTime call and knocked me off.

Dr. Pergam?

DR. STEVEN PERGAM: Thanks, Dr. Oster. I think this was a fantastic presentation to review. I have two questions, and hopefully, they'll be brief answers.

One is, in the distribution epidemiologically of myocarditis in kids, interestingly, that 5-to-11 group is the lowest rates in general with myocarditis. Can you speculate sort of the reason why that is

specifically that that's lower in the general population with standard, sort of typical myocarditis?

And then number two is I just want to be clear: you're talking about myocarditis, and then there's this sort of subgroup of pericarditis. For the discussion that you're bringing up for us, are you bringing those two together? Are the reviews including both of those, or is that a separate entity in terms of how you all look at this?

DR. MATTHEW OSTER: Great. Okay. So, first, for the epidemiology in kids, there's lots of different, I guess, theories as to why that can be. I think one of the biggest theories is that their testosterone and hormones play a big level in this, which is part of the reason why you may see a really high peak in adolescence and young adulthood, especially among males.

So, I think people still want to learn that, and does that differ also for the different types of myocarditis?

In terms of myocarditis and pericarditis, yes,

both have been reported, and sometimes the symptoms and presentation can overlap. So, we tried to come up with some definition. Certainly, sometimes someone will meet definition for both, and, in which case, we'll call them myopericarditis, inflammation of both areas.

For these numbers, though, we included those who had myocarditis or myopericarditis, and not just pericarditis. But pericarditis numbers are not nearly -- they don't jump out nearly as much for the young adults, and as a safety signal, most certainly some cases for sure. But it doesn't have the same impact in terms of numbers, nor for the long-term outcomes. But it is important to keep in mind that that has been seen as well.

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

DR. CODY MEISSNER: Thank you, Dr. Monto.

And thank you, Dr. Oster, for this presentation because I think this is a principal concern that people have regarding use of these mRNA vaccines in children. So, your presentation was very clear, and it was very helpful.

I would like to go back to the issue of late-phase gadolinium uptake on the MRI scan. My understanding is gadolinium is very sensitive for any inflammation in the heart. But the adult cardiologists say that a late-phase uptake, as you pointed out, is associated with further complications in life or, as you noted, sudden cardiac failure and death.

So, my question is do we have any experience with late-phase gadolinium uptake in children from other types of myocarditis and what sort of a prognosis that affords us in terms of what might be expected? And then, secondly, in adults who have late-phase uptake, how long is the interval of time before they begin to run into problems with heart failure? Thank you.

DR. MATTHEW OSTER: Sure. So, yes, you've touched upon a field that I can't even get all the cardiologists in my practice to agree on, and it's definitely a controversial field in the -- what is the meaning of the finding that we see? And I can tell you a couple of things about it.

So, first, yes, especially in adults -- not so much in kids -- it's been studied well in terms of its impact on longer-term outcomes. One thing, though, that people do like to see is improvement in this and resolution of this.

We often see, even still, a little bit of uptake, but everything else is normal; there's no active inflammation. The function is normal. You know, kids, their exercise test can be normal. Their (inaudible) are normal. Everything else will be normal, and all we have is this little signal that you see in the MRI that's there but, comparing to prior MRIs, isn't as impressive. So, what do we make of all that? And I think that's an area still ripe for investigation.

In terms of progressing and progression, I will say I hesitate a little bit to compare everything and say what those are because I really think of these diseases as same name but maybe different kind of entities and mechanisms. Certainly, some of the data I showed there for longer-term outcomes, adults have the

higher mortality when you have acute myocarditis, whereas kids tend to bounce back a bit better.

Will we continue to see that with others? Probably. I will say, you know, I showed you the MIS-C outcomes. We, as a field, have all been very pleasantly surprised to see how well these MRIs have looked in the kids after MIS-C. We'll see what we find after the vaccine-associated myocarditis.

DR. CODY MEISSNER: Thank you.

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

DR. ERIC RUBIN: Thanks. That was fascinating, Dr. Oster. And maybe this is a little bit of a follow-up on Dr. Meissner's question, but you were comparing classic myocarditis and its outcomes with what might be happening with vaccine-associated disease. And classic myocarditis, I know, in adults is often associated with direct viral infection of the myocardium or rheumatologic diseases and inflammatory (audio skip).

What do we know from the small amount of biopsy and pathology materials from the cases in

children that might tell us anything about underlying mechanism and might make us more comfortable with the predictions that you can make from the classic myocarditis cases?

DR. MATTHEW OSTER: Yeah, I wish I could give you a good answer to that. But what I can tell you is -- and I just looked at this yesterday -- of those about 800 or so, 800 to 900 cases, that we've called myocarditis, I think, like, one or two have actually had biopsies. Biopsy is not routinely used, especially in younger adults and in this population.

So, unfortunately, I can't talk about that. A number of the adults at least went to CAF to rule out a myocardial infarction, but they didn't necessarily grab a biopsy, or at least if they did, it wasn't reported to CDC. So, I think we don't know yet, but it'll be fascinating to learn more about it.

DR. ARNOLD MONTO: Thank you. Dr. Kurilla?

DR. MICHAEL KURILLA: Thank you, Arnold.

Yeah, Matthew, while we seem to see the most of the myocarditis after the second dose, I'm curious

about if there's been any close examination of those individuals experiencing myocarditis after their first dose of the vaccine. Do they have evidence of prior COVID infection, and specifically a recent COVID infection?

And then, related to that, do we have any data coming out of, let's say, the U.K., where they've played with a longer dosing interval between the first and the second dose? Is it the closeness of the dosing interval, the shorter dosing interval, that actually influences that rate of myocarditis that we see after the second dose?

DR. MATTHEW OSTER: Yeah, those are both excellent questions. For the VAERS data, we did not specifically separate out exactly the dose 1 or dose 2 yet. When we briefly looked, we didn't see a huge difference in their basic demographics. And we didn't feel like we had good information about whether there was actually a prior COVID infection.

That data is just not routinely reported to us, or it's not known. As you heard earlier, large

number of this population who have COVID-19 infection didn't know. Some places are starting to try to collect, for instance, nucleocapsid antibody when those kids come in, and try to look at that and figure out some more.

There have been some anecdotal reports that yes, maybe there was a prior infection. Of course, that doesn't give us any information about the timing whatsoever. But I know there are some more rigorous and robust studies that are being planned, so hopefully, we can answer some of those questions. And then I think your other question was prior --

DR. ARNOLD MONTO: Okay.

DR. MATTHEW OSTER: -- the timing? Yeah, we really don't have much information on the timing of the prior -- oh, and in the U.K., there has not been much released yet, but we are very interested to learn it. Most of the stuff that's come out for myocarditis that's not from the United States has been from Israel, but also some other countries as well. But they didn't necessarily have different dosing regimens. But it

will be interesting to see.

DR. MICHAEL KURILLA: Okay. Thank you.

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

DR. HAYLEY GANS: Thank you very much. I really appreciated that, obviously, because I had my previous question. My question this time -- because you did a very nice job in answering. Thank you very much.

My real question this time is -- this age group that we're considering right now, the younger age group, are the highest risk for MIS-C as opposed to the myocarditis. We saw that there is a drop in all the things that you explained to us.

So, there seems to be a very phenotypic difference between the MIS-C cardiac effects versus the post-vaccine cardiac effects, which you related mostly to the pre-COVID myocarditis. And I'm wondering -- this goes to the pathophysiology question that was already asked and what we can predict from vaccination in this particular age group. What would be their risk in terms of the cardiac effects?

So, I'm wondering if you could think through a little bit of that in terms of the different phenotypes of the post-vaccine myocarditis, which seems to be very different, and we know MIS-C itself has a particular phenotype. But that's what this age group is particularly high risk for, and how that could be impacted by vaccination.

I think (audio skip). I get we don't have data on that, but we do have some speculation about the differences about the physiology of those.

DR. ARNOLD MONTO: Yes, please. Can you speculate?

DR. MATTHEW OSTER: I will try my best while staying in whatever bounds I can. So, yes, you're right. We do think there are some differences, and it'll be hard to predict what we will see here. We'll certainly be watching it closely.

Regarding MIS-C, I will say, since there's some overlap in this age group -- there's been over 5,000 cases of MIS-C, and CDC is certainly monitoring for all vaccine safety efforts. And something when

vaccines first came out, that question that you posed was certainly of interest. And so, CDC has been actively looking for, are there cases of MIS-C that are associated all with vaccination? What do we see?

And we're not really seeing a big signal yet, at least in the 12-and-older group. CDC has identified, to date, 24 persons who received COVID-19 vaccine and then had an illness that met the CDC MIS-C case definition. Eighteen of these had evidence of past or recent SARS-CoV-2 infection, so follow-up from the question earlier. Six didn't.

And the definition for MIS-C is very broad. But important to note is there's no pattern that's really emerged either in the clinical features or the timing of onset or some of the demographics. So, we're still watching it and seeing it, but no patterns emerged like those for myocarditis where the very early pattern quickly emerged.

What's going to happen in the younger age group? We're going to be very active and very interested in learning that. But I'm reassured that we

haven't seen high rates of MIS-C associated with vaccine in any of the older kids.

DR. ARNOLD MONTO: Thank you. Dr. Nelson for the final question before our shortened break.

DR. MICHAEL NELSON: Thank you, Dr. Monto.

And thank you, Dr. Oster, for an outstanding presentation really acknowledging the complexities and really the data gaps with respect to the long-term outcomes of individuals affected. I have, hopefully, two quick questions for you.

One is, are there any ethnicity or social determinant-of-health trends with respect to the outcomes and timing of presentations for these patients affected either by COVID-19 disease or vaccination? The second one has to do with looking at the degree or type of data that's been acquired. From my observation, most of this data appears to be passively acquired through VAERS and other reports or active surveillance of codes for acute presentations.

And I do have a concern that there are many cases that are milder forms of myocarditis disease that

don't make it to the hospital and are not reported. So, my question for you is are there any -- speculating again -- differences that you would expect with COVID-19 disease and/or vaccination pre-hospital or milder forms of disease, and are there any data with respect to longer-term outcomes for these milder forms that could pose a concern for this age group?

DR. MATTHEW OSTER: Okay. Excellent question. So, first, yes, at some of the race and ethnicities and what are we seeing, you heard earlier about differences in COVID-19 and MIS-C. And I will say we published a paper looking at MIS-C and found that those higher risks in non-Hispanic Blacks actually exceeded what we would expect their numbers to be if it was all attributable to just their increased numbers of COVID-19.

So, it's almost like a double hit. It's the higher numbers amongst the non-Hispanic Black population, but then, even so, a higher risk of developing MIS-C. Obviously, the etiologies of that are unclear. For Hispanics, with the higher rates of

MIS-C, it seemed to be explainable by their higher numbers of COVID-19 that then led to higher rates of MIS-C.

For post-vaccine myocarditis, the data on race and ethnicity is not as complete as we would like it to be. I will say that the largest percent of people that have been reported have been white, but we need to take that in the context of what vaccination numbers are.

So, I think it's too early to say risks associated -- racial and ethnic disparities until we eliminate first some of the racial and ethnic disparities in terms of just overall vaccination because we can't really look at the outcomes until we cross that barrier.

In terms of identifying cases and how their cases are identified -- so, yes, VAERS is passive reporting. So, there's always a risk and concern for overreporting and underreporting. I will say I don't think overreporting is a big issue, because about 90 percent of the cases, with the information, they're able to be fully adjudicated. Underreporting can

certainly be a concern.

But there are other systems, and they all kind of work in tandem to look at it from different aspects. Vaccine Safety Datalink, from the data I showed, does do pretty active surveillance and looking at charts. It's not just ICD codes or discharge numbers. Some of the other systems, as well, try to incorporate that as much as able. So, each different way of looking at it has their advantages and disadvantages.

In terms of the milder cases, though, that don't present to care, for sure, that is a worrying concern. And I can say just in my own practice, though, once this all came up, we had a few kids referred to us who -- the parents said, oh, wow, they may have had something right after this. Was this myocarditis? And then we did an evaluation for them in the office and even did some other testing where there was any abnormalities noted.

So, could that be happening? Potentially, but I think now, at least it's on people's radar. And at least if the pediatrician or healthcare provider

becomes aware of it, they're trying to refer the kids to the appropriate care and evaluation.

But what do the outcomes mean in terms of a mild case versus not? I don't know. I don't think we have good information on that. I know, certainly, some of the other larger studies that are planned will try to get at that as much as possible. In kids, it can sometimes be a little bit harder even to identify it because they don't often identify chest pain. Case definition does allow for other symptoms to be present.

But we'll need to watch and see how they look and how they do.

DR. MICHAEL NELSON: I think that's been part of my frustration is that the clinical studies do not solicit the exact symptoms associated with myocarditis and pericarditis, and we're relying on patients presenting. It is an area for future study. Thanks again for your (audio skip).

DR. ARNOLD MONTO: Okay. Thank you very much. Very important discussion and questions.

We're going to take a 12-minute break. We're

going to start five minutes late at 10:50 Eastern Time, and I think we'll make up for the time by cutting into our lunch a little bit.

Okay. Ten-minute break now.

MR. MICHAEL KAWCZYNSKI: All right. Just a ten-minute break.

[BREAK]

SPONSOR PRESENTATION: BNT162b2 (PFIZER-BioNTech COVID-19 VACCINE) – REQUEST FOR EMERGENCY USE AUTHORIZATION FOR INDIVIDUALS 5 TO < 12 YEARS OF AGE

MR. MICHAEL KAWCZYNSKI: Good morning. Good afternoon depending upon where you are and welcome back from that break. I am Mike Kawczynski, and this is our 170th meeting of the VRBPAC. Now, just as a reminder to everybody, momentarily we may -- because we do have a lot of members that are in some areas that are having some different weather conditions, so please know we may have to do some unscheduled pauses if that does

happen. That being said, so far things have been running pretty well. I'm going to now hand it back to our chair, Dr. Monto. Dr. Monto, are you ready?

DR. ARNOLD MONTO: I am. I'm going to introduce Dr. Bill Gruber, who is the senior vice president for Vaccine Clinical Research and Development at Pfizer who will give the sponsor presentation. Dr. Gruber.

DR. WILLIAM GRUBER: Thank you, Dr. Monto and members of the Committee. Good morning. I'm pleased to present to you today the Pfizer-BioNTech BNT162b2 vaccine request for emergency use authorization in individuals 5 to less-than-12 years of age. My name is Bill Gruber, and I head the Vaccine Clinical Research and Development group at Pfizer.

My presentation this morning will be brief and to the point. Although I will touch on each of the topics shown here, I will focus primarily on the clinical data that demonstrates clear and compelling vaccine safety and efficacy and supports an emergency use authorization in 5- to less-than-12-year-olds.

Pfizer-BioNTech are seeking emergency use authorization of a 10-microgram dose of BNT162b2 for use in children 5 to less-than-12 years of age. A lower dose of 10 microgram was selected as the optimum dose for 5 to less-than-12 years of age based on the favorable reactogenicity profile and robust immunogenicity results from a dose finding in Phase 2/3 study. The proposed indication is for the active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 5 to less-than-12 years of age administered as a primary series of two doses of 0.2 milliliters each, three weeks apart.

I will share information with you today that the vaccine meets emergency use authorization guidance for children 5 to less-than-12 years of age. You will see that the vaccine meets all safety data expectations and meets immunobridging criteria and that 90.7 percent efficacy was observed. Plans are established for active follow-up of safety under emergency use authorization, and the vaccine's benefits outweigh its risks.

There's an unmet medical need for a safe and effective COVID-19 vaccine in children 5 to less-than-12 years of age. This was reviewed extensively by the CDC and will only be covered briefly on this slide.

In this age group, the cumulative burden of COVID-19 to date is at least 1.8 million cases. You've heard a figure of 1.9 million from the CDC presentation. With over 8,600 hospitalizations and 143 deaths, children of color are particularly vulnerable to COVID-19. COVID-19 causes additional long-term sequelae in children. There have been over 5,000 cases of multisystem inflammatory syndrome in children, or MIS-C, reported. Fifty percent of which have been in 5- to 13-year-olds. Sixty-seven percent of children experience symptoms greater than or equal to 60 days after COVID-19 diagnosis.

Severe outcomes are unpredictable and can occur in healthy children, prompting need for broad age-based vaccination. In fact, one in three hospitalizations occur among children without comorbidities, and you heard some of this again from

the CDC earlier.

MIS-C is unpredictable and can affect healthy children. Vaccinating children has other large societal benefits. For example, children likely play an important role in transmission, and vaccinating children can help reach herd immunity. Vaccination will help ensure in-person learning, which is critical for childhood development, by limiting community spread and school outbreaks. The need for a safe and effective vaccine for children 5 to less-than-12 years of age is clear.

I will share with you today clinical data that supports emergency use authorization for children 5 to less-than-12 years of age. I will highlight key points. Additional details are included in the briefing document.

We'll begin by looking at the experimental design of the vaccine study. This began with Phase 1 to identify a preferred dose level based on immune response and a safety profile. The 10-microgram dose, one-third the adult dose, was chosen because it had the

right balance between immune response and a satisfactory reactogenicity profile.

This 10-microgram dose was advanced into Phase 2/3 with a randomization scheme of two to one. Please keep this in mind when looking at both the safety as well as efficacy results. First group of safety information includes approximately 1,500 individuals that received the vaccine versus 750 that received placebo. At the request of the FDA, we've also enrolled approximately 1,500 additional individuals who received vaccine and 750 placebo receipts, most of whom have at least two weeks of safety data after dose 2. Non-inferior immune responses have been established comparing responses in children 5 to less-than-12 years of age to individuals 16 to 25 years old from the pivotal Phase 3 study.

Although not required for emergency use authorization, COVID-19 surveillance was conducted permitting evaluation of vaccine efficacy.

This represents the Phase 2/3 timeline of participants in this age group. This scheme is similar

to the scheme for other populations in which the doses were administered 21 days apart. Reactogenicity data was captured for seven days. Non-serious adverse events were captured for a month. Serious adverse events were captured for six months.

To enhance possible detection of the rare event of myocarditis observed in adolescents and young adults should it occur, specific instructions were provided to investigators to be vigilant for symptoms and signs of this condition, including chest pain, and to perform work up in the event of suspected myocarditis. Blood draws are obtained as shown to measure immune response.

As for nearly all our trials, we continue to obtain surveillance on the populations to look for the potential to demonstrate efficacy, and that proved possible in this particular trial.

This slide represents the two datasets that have been submitted to support emergency use authorization application. One is the initial cohort of 2,268 participants, for which the median follow-up

time is 2.3 months, shown as the top blue bar. In the later submission, follow-up of this group has been extended as shown in light blue. Findings did not differ appreciably and will not be discussed further in this presentation.

Additionally, later and represented by the lower bar graph, we also enrolled an additional cohort of 2,379 participants. In conjunction with the original cohort, this permits evaluation of a total of approximately 3,000 vaccine recipients to define rare events for at least two weeks for most of the 3,000 vaccine recipients and for two to three months for over 1,500 vaccine recipients in this submission.

I will first describe safety in the initial safety enrollment group.

Here are the demographics for the 5- to less-than-12-year-olds in the initially enrolled safety population. Demographics for the additional safety group and efficacy population are similar. You can see there was good representation in terms of gender, race, and ethnicity. The mean age of vaccination was in the

middle of the age span between 5 to 11 years of age at 8 years of age. More than 11 percent of the population had obesity as an underlying condition and comorbidities, including obesity, were represented in approximately 20 percent of the population.

Here are local reactions by maximum severity within seven days after each dose. Dose 1 is at the top. Dose 2 is at the bottom. You can see the reactions in the 5- to less-than-12-year-old age group compared to 16- to 25-year-olds. There is some increase in mild to moderate redness and swelling, both after dose 1 and dose 2, in the 5- to less-than-12-year-old age group. Pain at the injection site was comparable between the two age groups. In general, the local reactions meet a satisfactory safety profile.

Systemic events are shown on this slide by maximum severity within seven days after dose 2 in children 5 to less-than-12 compared to 16- to 25-year-olds. Reactions were typically higher in vaccine recipients. Dose 1 reactions tended to be less frequent and are not shown here.

The vaccine group is shown at the top part of the graph and the placebo group at the bottom. I draw your attention particularly to fever and chills. You can see that, if anything, the incidence of fever was lowered and mostly mild to moderate in individuals who were 5 to less-than-12 years old compared to the older age group. That was true for chills as well.

Likewise, across the other systemic event parameters, you can see that responses were comparable or less to those seen in 16- to 25-year-olds, again representing a satisfactory systemic reaction profile for 5- to less-than-12-year-old children.

Now let me review unsolicited adverse events. This graphic represents overall adverse events from dose 1. The initial enrollment group is shown at the top, and the safety expansion group is shown at the bottom. In both groups, you can see comparable levels of any adverse events or related adverse events.

There were very few serious adverse events and no related serious adverse events and no deaths. One female participant was withdrawn from the study due to

a fever of 40 degrees centigrade on day 2 after dose 1 accompanied by neutropenia. The fever resolved in one day. This child carries a preexisting diagnosis of benign neutropenia followed by a hematologist. She recovered uneventfully.

This represents adverse events occurring at an instance of greater-than-one percent by system organ class for this age population in the initial enrollment group. You can see comparable rates between vaccine receipts and placebo recipients whether we're talking about any adverse events or the categories specified underneath. This again reflects a satisfactory safety profile and events common to this age group. Lymphadenopathy has been infrequently observed in other populations after vaccine and was observed in 0.9 percent of vaccine recipients in this enrollment group.

This represents comparable analysis of adverse events in the safety expansion enrollment group. You can see similar rates between vaccine and placebo groups. Again, this reflects a satisfactory safety profile.

Serious adverse events from dose 1 to the cutoff date are shown here for both safety groups. All SAEs were considered unrelated. Three events are related to trauma and one related to ingestion of a foreign body. In the expansion safety group, one participant reported infective arthritis of undiscerned etiology 15 days after dose 1. It resolved 21 days later.

We followed participants for adverse events of special interest as designated by either the FDA or the CDC. Summaries for both enrollment groups are shown here. For FDA adverse events of special interest, no anaphylaxis, no myocarditis, no Bell's palsy, and no appendicitis were reported.

For CDC adverse events of special interest, angioedema and hypersensitivity were uncommonly seen, observed in both vaccine and placebo recipients, and were short lived. Rashes tended to be more after vaccine, uncommon overall, mild and short lived. One case of arthritis is the infective arthritis already described. The case of vasculitis is a reported case

of Henoch-Schonlein purpura considered unrelated that occurred 21 days post-dose 1. Follow-up is ongoing.

Safety conclusions for 5- to less-than-12-year-olds. Reactogenicity was mostly mild to moderate and short lived. Observed mild to moderate local reactions, redness, swelling captured by eDiary were more common, and systemic reactions including fever, less common than those in 16- to 25-year-olds. The observed AE profile in this study did not suggest any safety concerns for vaccination in children 5 to less-than-12 years of age. The database of approximately 3,000 enrolled BNT162b2 recipients provides a high degree of confidence for the following: rare events approximate to vaccination, such as myocarditis or anaphylaxis, are unlikely to occur at a rate of 1 in 1,000 or higher.

Now I'd like to turn to the examination of the immune response to the vaccine. Immunobridging criteria comparing the 5- to less-than-12-year-olds to 16- to 25-year-olds were met both for the geometric mean ratio and for seroresponse as shown on this slide.

At the top is represented SARS-CoV-2 neutralizing antibody titer. You can see the geometric mean titers represented after the second dose in the middle two columns in blue. The geometric mean ratio of 1.04 is shown on the right-hand side with a lower bound of the confidence interval well above the 0.67 criterion.

The observed GMR was above the prespecified criteria of 0.8 and also above the GMR of one requested post hoc by the FDA. In addition, seroresponse rates are shown at the bottom. You can see the seroresponse rates were virtually identical in 5- to less-than-12-year-olds compared to the 16- to 25-year-olds at 99.2 percent a piece. This criterion was also met with a lower confidence bound of minus 2 percent, well above the minus 10 percent that was required.

It was also important and requested by the FDA for us to look at responses to the Delta variant given its prominence as a cause of COVID-19. Much as we have seen in older populations, the responses were quite robust, not only to the wild type, shown on the left side but also to the Delta variant on the right in the

subpopulation of 34 individual study. Note the comparable postvaccination titers at one month for wild-type vaccine strain and for the Delta variant with high geometric mean fold rises shown at the top. This comparable response predicts efficacy for 5- to less-than-12-year-olds during a time when the Delta variant is prominent.

High efficacy against COVID-19 was in fact overserved when examining COVID-19 occurrence from seven days after dose 2. Remembering that the randomization in this study was two to one vaccine versus placebo, the case split of 3 to 16 with surveillance times shown yields an efficacy of 90.7 percent with a high degree of confidence shown. No severe cases of COVID-19 or multisystem inflammatory syndrome in children were reported in either group. Note that cases occurred in July through September, when the Delta variant was the most prominent variant in circulation.

At this time, 14 of 19 samples have been successfully sequenced, and all yielded the Delta

variant, confirming high efficacy against this highly transmissible strain of SARS-CoV-2. This data is yet to be submitted to the FDA.

This curve shows the cumulative incidence of all available COVID-19 cases beginning after dose 1. The mean length of follow-up time after dose 2 is 3.3 months. Placebo cases are in red, vaccine cases in blue. Efficacy was durable for this period of follow-up to date, and surveillance is continuing.

Let me summarize the immunogenicity and efficacy conclusions. Immunobridging success criteria were met for 5- to less-than-12-year-olds compared to 16- to 25-years-olds. Vaccine-immune sera effectively neutralized both the wild-type vaccine virus as well as the highly transmissible Delta variant of concern. BNT162b2 as a two-dose series demonstrated high efficacy against COVID-19 in this population of 5- to less-than-12-year-olds when the Delta variant was prominent.

Pharmacovigilance activities are a critical component of activities to detect unexpected safety

events rapidly. Pfizer continues to conduct robust pharmacovigilance activities and collaborate with regulators and international groups. Proactive risk mitigation activities, such as labeling, educational materials, and bio differentiation will continue. Pharmacoepidemiology studies will include children 5 years and up to evaluate for myocarditis occurrence and sequelae as well as other possible rare adverse events. This includes one study that will follow up identified U.S. postvaccination myocarditis/pericarditis cases for five years within the Pediatric Heart Network.

What are some of the key things that have been learned about myocarditis that inform the positive benefit-risk of the Pfizer-BNT vaccine? As we have learned from publications, government public health websites and the previous presentations from the CDC, myocarditis is typically caused by viral infections. SARS-CoV-2 is one such example. COVID-19 patients have nearly 16 times the rate of myocarditis compared to individuals without COVID-19. In rare cases, myocarditis is observed after COVID-19 vaccination in

children and adolescents.

This occurs more frequently after the second dose and in males. The acute clinical course is generally mild, resolving with conservative treatment. Rates of post-vaccination myocarditis in 12- to 15-year-olds appear lower relative to older adolescents in both the United States and Israel.

In this context, benefit-risk assessments supports a revision to the emergency use authorization for the vaccine to include children 5 to less-than-12 years of age. This is based on model-predicted benefit-risk outcomes per million children vaccinated over six months.

You've heard some of this from the CDC, and information is also included in the Pfizer and FDA briefing documents. Please keep in mind that this projection of benefit-risk assumes the rate of myocarditis in 5- to less-than-12-year-olds that is equal to that of 12- to 15-year-olds, which may be an overestimate. Why? Rates trend downward in younger adolescents compared to older adolescents. This

downward trend may extend to children less than 12. In addition, the lower 10-microgram dose and lower common systemic reactions in children 5 to less than 12 may also result in a lower risk of rare adverse events like myocarditis.

This table displays FDA Scenario 4 which appears to better match, given the 90.7 percent observed clinical trial efficacy in 5- to less-than-12-year-olds. This scenario assumes the COVID-19 incidence rate of September 11th, 2021. This incidence rate is a good choice because we may see it yet again if children are not vaccinated due to the looming winter respiratory disease season and unpredictable nature of pandemic spread. COVID-19 outcomes prevented versus excess myocarditis case risks are displayed. The CDC VAERS and VSD myocarditis case estimates have been described previously.

Note that the VSD result may be inflated by virtue of including 16- to 17-year-olds at the peak of myocarditis incidence compared to lower rates seen in younger adolescents. VSD rates are based on cases

observed in a network of health systems where case confirmation is performed via medical chart review. VAERS included cases reported to the FDA that have, at least to some extent, been medically confirmed. This confirms some specificity to the diagnosis of myocarditis.

In contrast, the FDA briefing document model relied on a non-chart-confirmed cases from a U.S. healthcare claims database, OPTUM, as a worst-case scenario. This, therefore, lacks potential specificity, and the FDA document acknowledges that the 106 value may be an overestimate.

However, even if myocarditis rates in children 5 to less than 12 are the same as younger adolescents regardless of which adolescent myocarditis rates we choose, the corresponding benefits exceed the risks. For every one million children vaccinated, the number of cases and hospitalizations prevented exceed any of the myocarditis estimates.

ICU admissions prevented exceed both CDC myocarditis estimates. Vaccination is also likely to

confer additional benefits, including reduced transmission, improved herd immunity, and increased in-person learning, supporting child development. In such a case, the benefit becomes all that more substantial compared to the risk.

Hence, Pfizer-BioNTech requests emergency use authorization of BNT162b2 for active immunization of individuals 5 to less-than-12 years of age administered intramuscularly as a series of 2-microgram doses, three weeks apart.

We want to thank all of those who made this possible, the clinal trial participants and their families foremost, sites, investigators, CRO, our partners and their staff, and the FDA guidance to help us assess and address this urgent medical need. Thank you and I'm now prepared to respond to questions.

With the indulgence of the chair, we might begin with the first question that Dr. Meissner asked about the use of buffer. But I defer to the chair.

Q&A SESSION

DR. ARNOLD MONTO: Go ahead and answer it, Bill.

DR. WILLIAM GRUBER: Thank you, Dr. Monto. Also, I'll start and then I'm going to ask Nick Warnie to provide some of the details. As indicated in, I think, the FDA presentation, the buffer was changed to confer additional stability as a minor change that will also actually improve shelf life. I think Dr. Meissner had asked the question, actually how does the buffer work and perhaps how it was chosen. Nick Warne will provide some of the details. Nick?

DR. NICK WARNE: Thank you, Dr. Gruber. My name is Nick Warne, and I'm in biotherapeutics and pharmaceutical sciences.

We've explored a number of alternate buffer systems to enhance the stability of the RNA LNP product as well as to allow for lower concentrations to be made available. The switch from phosphate to tris demonstrated better refrigerated stability and

increased from 31 days out to 10 weeks as well as it enabled us to dilute the product from 0.5 milligrams per mL to 0.1 milligrams per mL, making it easier to prepare the dose.

Tris is a precedented buffer in biotechnology and has been used in at least three vaccines. Our decision was based on empirical stability data, manufacturability, and ease of use for pharmacists and healthcare professionals. We prefer not to speculate about the underlying chemistry. We have performed an extensive comparability evaluation comparing the two formulations and have found them to be biochemically and pharmaceutically comparable.

Please note that the manufacturing process of the RNA active ingredient and the lipid nanoparticle is completely unchanged. The only change is in the formulation, which is the last step of the product manufacturer. Again, there is no change to the active ingredient.

DR. ARNOLD MONTO: Thank you. We'll go on to Dr. Offit.

DR. PAUL OFFIT: Thank you, Dr. Gruber. One of the questions already starting to come up were -- if this vaccine were to be authorized -- from parents of, say, children who are 11 years old, they have been asking, should we just wait until they're 12 and get the larger dose?

My question to you is, did you break down sort of the geometric mean titer for neutralizing antibodies in, say, the 10- to 11-year-old versus 5- to 6-year-old? Was there any difference there? And then does it correlate to that of the three children who, despite getting vaccinated, still developed mild COVID? What were their ages? Thank you.

DR. WILLIAM GRUBER: Let me address the first question about the nature of the antibody responses based on age. If we can bring up Slide number 1, please. While I'm doing that, if we can address the ages of the -- some of the notes on the individuals that we had breakthrough infection. I think you can see represented here. This represents geometric mean titers by age subgroup in the subjects 5 to less-than-

12 years of age. On the left-hand side, you see the entire group. Then as you walk through, you see the individual groups by very narrow age breakdown.

I think it's easy to appreciate, recognizing that the left bars represent preimmunization, right bars represent one month post-dose 2, that there really is a comparable response across the age groups that we are confident that the dose works well across the entire age group. The three cases in the BNT162b2 group that you asked about were 10 and 11 years old. I am mindful of, actually, the highest tack rate in the placebo group was also, I think, over 50 percent in cases as I recall were in that age group.

That may be more a feature of the fact that that group seemed to have more potential exposure, which may make some sense given that these children begin to socialize more as they get older. Did that answer your question, Dr. Offit, and anything else?

DR. PAUL OFFIT: That answered my question.

DR. ARNOLD MONTO: I'll just turn that question upside down and say, what would happen if you

gave a lower dose to a 12-year-old --

DR. WILLIAM GRUBER: I'm sorry. Could you repeat that? You broke up.

DR. ARNOLD MONTO: -- in terms of antibody and in terms of side effects?

DR. WILLIAM GRUBER: I'm can you just say that again. I'm sorry. I'm not sure I completely understood the question, Dr. Monto.

DR. ARNOLD MONTO: What would happen if you gave the lower dose to the 12- to 15-year-olds in terms of antibody response and perhaps reduction in side effects?

DR. WILLIAM GRUBER: That becomes a logical question. Obviously, based on the experience that we now have in 5- to 11-year-olds, you'll recall that when we presented the data to the FDA -- for those of you that have reviewed that data -- we had higher antibody responses at the 30-microgram dose in individuals who were in the 12- to 15-year-old age group, and that conferred a high level of efficacy. There is the potential, although we don't have the data to show it,

for a 10-microgram dose to provide antibody response. We have some possibility of looking at that in the future, but we don't have that data today.

DR. ARNOLD MONTO: All right. You are thinking about looking at that?

DR. WILLIAM GRUBER: Yes, we are thinking about that as a potential option, particularly as we move out of the pandemic period.

DR. ARNOLD MONTO: Right.

DR. WILLIAM GRUBER: The key goal right now is obviously providing protection with a safe and effective vaccine to get ahead of the pandemic. Obviously, the 30-microgram dose has now been used. (audio skip) to get evidence that it is working to provide effectiveness.

DR. ARNOLD MONTO: Agreed. I violated a principle of asking a question about something that might be partially settled right now. Dr. Pergam.

DR. STEVEN PERGAM: Thanks, Dr. Gruber. A couple of questions. Just to get back to the tris versus the PDS in the study, was the actual study done

with the PDS version of the vaccine? Was the tris version given in the actual trial? That's the first question. The second question is I've seen some images, but I just want you to clarify. For the public, when these different dosing strategies are being used, is the image or the look of the bottles going to be different so that it's easier to assure that there's not misdosing among children?

DR. WILLIAM GRUBER: Nick Warne's coming up, and we actually have a slide to again represent the image not only of the bottle but the nature of (audio skip) the cap but also the label that I think will answer that question.

The answer to your first question is that the studies were done using the same volume, 0.2 milliliters, that is in the final presentation in terms of the dose but contain the PDS buffer. We obviously had extensive consultations with the FDA, and it was determined that the clinical studies were not required, again, because the LNP and mRNA are the same and the behavior in terms of reactogenicity and efficacy are

expected to be the same. Let me ask Dr. Warne to address the other question about the presentation.

DR. NICK WARNE: Thank you. If could have Slide 2 brought up, please. In terms of vial differentiation, we have made substantial efforts to differentiate the pediatric 5- to 11-year-old vial from the currently available vial. You can see the images on your screen. On the left, you have the current vial that's available with the purple cap, purple label. It's quite distinct from the pediatric dosage form, which has an orange cap and an orange label. Similarly, the packaging, the actual cardboard box in which the product will be received, is orange.

The large carton, the shipper carton, that is received at the pharmacy will also have an orange label on it. We have tried to maximize as best we can the number of ways we can differentiate the pediatric dosage form from the current dosage form.

In addition to product differentiation, the instructions for use will be distinct. Also, you can see on the screen we have a different dilution scheme

in the pediatric product versus the current product which will allow ten doses per vial at ten micrograms.

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

DR. OFER LEVY: Thank you, Dr. Gruber, for the presentation. An important element of consideration is whether the Pfizer mRNA vaccine may be able in some fashion to reduce transmission of Coronavirus infection. It was alluded to in your slides as likely. Maybe I'm paraphrasing something along those lines. What data does Pfizer have, not just in this age group but other age groups, at this point in time to demonstrate an impact on transmission?

DR. WILLIAM GRUBER: Thank you, Dr. Levy. Within the 1007 trial, we did not specifically look at the potential for asymptomatic disease and therefore the potential for transmission in that setting. However, we are well aware, and I think the Committee's well aware there's a great deal of real-world evidence that supports that vaccination impacts transmission in adults. The notation really is that, by virtue of showing a non-inferior immune response from children to

adults where we demonstrated efficacy as well as the high level of efficacy that we demonstrated in the 1007 study, that it's reasonable to expect that there'll be some reduction in transmission for children having asymptomatic disease or for the potential for asymptomatic spread.

I think it's also worth remembering that just prevention of symptomatic disease in its own right prevents those children from potentially being in a school-room setting and transmitting in that circumstance. You heard from the CDC earlier that children do appear to be an important mechanism of transmission to other children as well as to the community.

On balance, I think whether we're talking about asymptomatic disease and transmission where we can bridge to where that's proven to be the case or just the nature of reducing symptomatic children from ending up in the schoolroom (audio skip) potential for affecting community spread seems very real.

DR. OFER LEVY: Thank you.

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

DR. PATRICK MOORE: Thank you. That was a very nice, clear presentation. I'd like to follow up on Dr. Levy's comment. As you said, if we have real, clear data that this vaccine prevents transmission, that would be a very important positive benefit in a population that has a low risk of serious disease. Also, the second point is your company, Pfizer, makes the vaccine PREVNAR, which is a conjugate polysaccharide vaccine as you know. The unconjugated polysaccharide vaccine does not prevent transmission at all. It's very effective at preventing invasive disease, but it has no effect on transmission. Conjugated vaccine does.

So where does this vaccine lie between those two poles? And I think you have the data that you can actually look at that. If you were to look at your visit two, V2, and your visit five blood draws, you would have a randomized, blinded controlled study that would allow you to look at at least antibody titers that would give you an idea as to whether there was

viral invasion let alone symptoms in the vaccinated population. I'd urge you or perhaps request FDA to urge you to make that test. Since you have those blood, you have all the materials, it does not require any additional visits, just a single blood test that could potentially give us an answer.

DR. WILLIAM GRUBER: I thank you, Dr. Moore. Let me deal with the last question first, and obviously, we'll take that under advisement. I think we've thought about doing that, not only in this population but other populations as well, to look for the potential for interference with asymptomatic disease and then the potential for reduction in transmission.

Regarding the first point, obviously, as you're well aware, we are quite familiar with the nature of the conjugated polysaccharide and what it brings to the table in terms of immune response. You're absolutely right. The polysaccharide vaccine without conjugation to a protein essentially is a T cell-independent antigen. It doesn't produce memory.

I think one of the things that is gratifying, whether we'll actually impact transmission, I guess, remains to be seen. But we have evidence that this vaccine produces not only CMI but evidence that it likely produces memory. Some of that's from the laboratory studies but also from the fact that, I think, there's at least supporting evidence that although antibody declines, protection seems to persist greater than the decline in antibodies.

If memory is important, which it may well be on re-exposure to the virus in terms of preventing transmission, then I think this comes closer in that respect to the conjugate vaccine than it does the polysaccharide.

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

DR. MICHAEL KURILLA: Thank you, Arnold. This is a two-parter. Don't know why my camera's not working at the moment. I'll just reiterate some of the previous comments related to the asymptomatic and transmission. It's clear that the younger the infected individual, the more likely they are to have an

asymptomatic infection. And I think, in terms of this population, it's at least 50 percent. I would assume, as we've seen with the adults, that, upon vaccination, it's going to go higher than that. So you may be actually missing, by just looking at symptomatic disease, the degree of vaccine efficacy in terms of preventing overall infection.

I think that's one major impact. The other question I really wanted to pose to you is you have very limited data at this point in time because of not much follow-up. Is there any reason to believe that the antibody decay kinetics in this population is going to look any different from what we've seen in adults? Is the expectation that these children are going to need a boost in six months, and how do you think that's going to play out with -- because, if the focus is on immunobridging and the antibody response, then, if the antibodies wane at the same level, then the argument would be is we need to maintain their antibody levels.

Yet, we're seeing in younger populations better holding up of protection for the serious disease

that's been commented on in terms of hospitalizations and worse. Comments?

DR. WILLIAM GRUBER: Thanks, Dr. Kurilla. In terms of your first question, obviously a good question about the nature of being able to look at asymptomatic infection. Like Dr. Moore's question before, we'll look into the potential of looking serologically at that.

As far as the second question in terms of antibody decay, you may recall from the slide that I showed that we intend to get antibody responses out at six months, which maybe give us, of course, an early clue as to the potential for waning immunity and protection.

Much has existed for the other populations, particularly adult populations. The real-world evidence seems to be so robust and catches up so quickly that my expectation is we'll gain information from that as well to determine the durability of response. I'm encouraged by the fact that we're starting off, at least, essentially at the same point

that we do in adults with efficacy greater than 90 percent. So I'm expecting the given potential to produce memory (audio skip) cell mediator even (audio skip) that that will (audio skip) protection.

DR. MICHAEL KURILLA: But do you have any idea if the lower dose you're giving the children provides an equivalent stimulation to the memory as opposed to just antibody levels?

DR. WILLIAM GRUBER: We don't have that specific data. But again, I think the level of efficacy certainly is comparable to what we've seen.

DR. MICHAEL KURILLA: Thank you.

DR. ARNOLD MONTO: Dr. Hildreth. This is going to be our last question before the FDA presentation. I want to remind everybody that we will have another question and answer period for both the sponsor and the FDA after lunch. So this is not the last question that you may receive, Dr. Gruber. Dr. Hildreth.

DR. WILLIAM GRUBER: I'm ready for this afternoon.

DR. JAMES HILDRETH: Thank you, Dr. Monto, and thank you, Dr. Gruber.

When you did your risk-benefit assessment and your bridging document, there were six scenarios that you considered. It strikes me that Scenario 3, where you have the incidence from, I think, it's, June of 2021 where the cases are low, the hospitalizations from myocarditis actually exceeded hospitalization from COVID-19.

As we get more adults vaccinated and we see the Delta curve waning, isn't it likely that that's going to be the more likely scenario versus the highest incident that you have in your assessment?

Could you comment on that because, to me, the single most important question is whether the benefits outweigh the risk? In that scenario, they clearly don't. Can you comment, please?

DR. WILLIAM GRUBER: Sure. We obviously looked across all the six scenarios. You'll get a chance to hear that in some detail from the FDA's presentation. Our opinion in terms of Scenario Number

3 is it actually picked the lowest rate of disease, which is actually lower than what's being experienced now. And I think if you just look at our track record in terms of predicting the epidemic, we've not done particularly well. Given that the winter season is coming, the Delta virus is still out there, you still have a large number of susceptible children, there's every reason to believe that the rate will not be at the later.

Let's suppose that it is. Even in the FDA briefing document, they talk about the fact that, despite that difference where now the number of myocarditis cases may exceed the benefits seen from the vaccine, and of course in a circumstance where you're assuming that that rate is the same as in 12- to 15-year-olds, that the other benefits, and particularly those societal benefits, obviously protecting vulnerable populations and including populations of color, the ability to get children back into the schoolroom setting -- I think as you know, many children depend on schools as a safe place as well as a

place to often get their meals.

All of those things I think have to enter into the equation regardless of the rate that says (audio skip). In our view, it's more realistic to think that the rate is going to be higher than that very lowest rate that's been (audio skip).

DR. JAMES HILDRETH: Thank you.

FDA PRESENTATION: FDA REVIEW OF EFFECTIVENESS AND SAFETY OF PFIZER-BioNTech COVID-19 VACCINE IN CHILDREN 5 THROUGH 11 YEARS OF AGE EMERGENCY USE AUTHORIZATION AMENDMENT

DR. ARNOLD MONTO: Thank you. Now we move to the FDA presentations. We have three parts to the presentation. I'll introduce each of the speakers individually. The first is Dr. Leslie Ball who will be talking about the FDA review of the Pfizer-BioNTech submission. She is a medical officer in the Division of Vaccine and Related Products Applications. Dr. Ball.

DR. LESLIE BALL: Hi, good morning. I'm Dr. Leslie Ball, medical officer and pediatrician in the Center for Biologics, Office of Vaccine Research and Review, Division of Vaccines and Related Products Applications at FDA.

I will be presenting FDA's review of the effectiveness and safety of the Pfizer-BioNTech COVID-19 vaccine in children 5 through 11 years of age submitted under the Emergency Use Authorization Amendment, or EUA.

I'd like to start off by acknowledging the many contributions of my colleagues.

I will start with the regulatory background of the product. I will next cover the design study submitted to support EUA, review the immunogenicity, supportive efficacy and safety results, and conclude with an overall summary.

The EUA under discussion today is intended to support the use of an intramuscular two-dose primary series of the Pfizer-BioNTech COVID-19 vaccine, 10-microgram mRNA each dose administered three weeks

apart. The vaccine composition is based on SARS-CoV-2 to spike glycoprotein (S) antigen encoded by RNA derived from the Wuhan strain. It is formulated in lipid particles.

COMIRNATY is the only vaccine that has FDA approval for the prevention of COVID-19 in individuals 16 years of age or older. FDA has issued five related EUAs previously, including the EUA for Pfizer-BioNTech COVID-19 vaccine to individuals 12 years of age or older with and without certain compromised immune systems and as a booster dose. Each dose contains 30 micrograms of mRNA.

In August of this year, the Pfizer-BioNTech COVID-19 vaccine, also known as its name during development, BNT162b2, was approved under a biologics license application. As I mentioned, the proprietary name is COMIRNATY with an indication of active immunization to prevent COVID-19 in individuals 16 years of age or older. The approved regimen is also a two-dose primary series, three weeks apart.

I'll discuss the study design. Study

C4591007, hereafter referred to as Study 1007, is a Phase 1/2/3 ongoing randomized, observer-blinded, placebo-controlled study in children 5 through 11 years of age. This slide provides an overview of the Phase 1, or dose-finding, portion of the study which evaluated the safety and immunogenicity of three dose levels at 10, 20, and 30 micrograms.

Formulation used in Study 1007 was the currently authorized formulation, PBS sucrose formulation, diluted with saline to the appropriate dose levels to administer the 10-, 20-, and 30-microgram dose levels. Phase 1 component took place in the U.S. and enrolled children who were not at high risk of SARS-CoV-2 exposure or severe disease and who did not have evidence of prior SARS-CoV-2 infection. Doses were evaluated sequentially with 16 participants per dosage beginning with the 10-microgram dose. SARS-CoV-2 50 percent neutralizing geometric mean titers, or GMTs, were assessed at seven days after dose 2.

A total of 48 participants were enrolled in this Phase 1 portion of the study. Safety review of

reactogenicity data from the initial four participants who received the 30-microgram dose for both doses found that all four participants developed mild to moderate redness at the injection site and fever to 38.7 degrees centigrade. The higher frequencies solicited adverse events. Note there were no SAEs in the study.

In participants receiving the 30- and 20-microgram doses, the favorable AE profile at the 10-microgram dose and the immunogenicity results demonstrating similar neutralizing antibodies at the 10- and 20-microgram doses informed the internal review committee's decision to discontinue the 30-microgram dosage and proceed to the Phase 2/3 study at the 10-microgram dosage. There were no SAEs or deaths, and no participants from Phase 1 withdrew or were discontinued from the study.

This is Study 1007 Phase 2/3 as being conducted in the United States, Finland, Poland, and Spain. This portion of the study did not exclude children with a history of prior SARS-CoV-2 infections, children with known HIV, hepatitis B or hepatitis C, or

stable preexisting disease. Participants were randomized two to one to receive two doses of 10-microgram vaccine or saline placebo three weeks apart.

Phase 2/3 component of the study consisted of two cohorts of equal size, approximately 22,250 each. A second cohort was added at the request of FDA with the intention of increasing the size of the safety database in children 5 through 11 years of age. The total size of the safety database consisted of approximately 3,100 children in the vaccine group. Immunogenicity was assessed in a subset of 322 participants in this study, and efficacy data was obtained through continuous surveillance for potential cases of COVID-19.

This slide depicts the timeline for Phase 2/3 Cohorts 1 and 2. Cohorts 1 and 2 vary by the duration of follow-up. The data from an additional 2,369 participants in Cohort 2 were submitted during the EUA review process. In Cohort 1, the first participant was enrolled by June 7th, 2021. The data cutoff was September 6th, 2021. This cohort included

approximately 1,500 vaccine recipients and 750 placebo recipients, of whom 95 percent combined had at least two months of safety follow-up after completing a two-dose primary series. Safety data from this cohort included solicited adverse events, unsolicited adverse events, serious adverse events, and AEs of special interest.

For Cohort 2, safety data from this cohort included the safety monitoring as in Cohort 1 but, due to the shortened follow-up time, focused on SAEs and AEs of clinical interest. Cohort 2, the first participant was enrolled on August 26th, 2021, and the data cutoff was October 8th, 2021. The cohort was approximately the same size as the Cohort 1, but the median duration of follow-up here was 2.4 weeks post-dose 2 at the time of data cutoff.

This slide depicts the study C4591001, or 1001 for short, which was used for the immunobridging analysis to support vaccine effectiveness in a 5- through 11-year age group. Study 1001 was the study in which vaccine clinical efficacy against COVID-19 was

established for individuals 16 years of age or older.

The comparator group was a subset of 300 randomly selected participants enrolled in Study 1001 Phase 2/3 who received the vaccine at the 30-microgram dose level in a two-dose primary series, 21 days apart.

This slide depicts the comparison that took place in the immunobridging analysis. Effectiveness of the Pfizer-BioNTech COVID-19 vaccine is being inferred by comparing neutralizing antibody responses against the Wuhan-like strain one-month post-dose 2 in children 5 through 11 years of age enrolled in the Study 1007 and comparing that to a subset of study participants 16 through 25 years of age enrolled in a separate study 1001. Participants in both studies had no evidence of prior SARS-CoV-2 infection.

Immunobridging endpoints and statistical success criteria will be discussed in the next two slides. There were two immunobridging endpoints. The first endpoint was GMT ratio. The important thing to note here was that that immunobridging success criteria consisted of the lower bound of the two-sided 95

percent confidence interval for GMT ratio with greater than 0.67, and the point estimate was greater than or equal to one.

The second immunobridging endpoint was seroresponse. Immunobridging success criteria required a lower limit of the 95 percent confidence interval for the difference in seroresponse rates 5 to 11 years of age minus 16 to 25 years of age of greater than or equal to minus ten percent.

This slide provides an overview of the analysis populations and the number of participants in each. Safety populations consisted of all randomized participants who received at least one dose of the study intervention. The size of the safety populations for Cohort 1 and 2 for the vaccine group are provided near the top of the middle column in blue.

The population considered in the immunobridging subset was the evaluable immunogenicity population without evidence of prior SARS-CoV-2 infection by history or testing. Evaluable efficacy population consisted of participants who received both

doses within a critical defined window.

This slide presents the demographics and baseline characteristics of Study 1007 Phase 2/3 Cohort 1. Demographics of Cohort 2 were similar and will not be shown. Overall, demographics included 52 percent males and 48 percent females. The mean age was 8 years in both groups. Regarding race, 78 percent were white; seven percent were multiracial. Approximately 6 percent were African American, 6 percent Asian, and 21 percent were Hispanic.

Ninety-one percent were without evidence of prior COVID-19 infection. Participants were enrolled in four countries that I mentioned: U.S., Spain, Finland, and Poland, with the U.S. contributing 71 percent of participants. Approximately 20 percent of subjects had comorbidities which included obesity in about 12 percent, asthma in approximately 8 percent, neurologic disorders in about 1 percent, and congenital heart disease in less than 1 percent.

Results for the GMT primary endpoint are displayed here. The important thing to note is that

the success criteria for immunobridging based on a GMT ratio were met as the lower bound of the 2-sided 95 percent confidence interval for GMT ratio was greater than 0.67, and the point estimate was greater than or equal to one.

Seroresponse rates among participants without evidence of prior SARS-CoV-2 infection up to one month after post-dose 2 were displayed here. The lower limit of the 95 percent confidence interval for the difference in seroresponse rate was minus 2 percent, which was greater than the prespecified margin of minus 10 percent, and thus immunobridging based on seroresponse rate was met.

In response to FDA's request for immunogenicity data to support the effectiveness of the 10-microgram Pfizer-BioNTech COVID-19 vaccine primary series against the Delta variant, Pfizer submitted exploratory analyses from a randomly selected subset of participants from the evaluable immunogenicity population consisting of 34 vaccine and 4 placebo recipients who did not have evidence of prior SARS-CoV-

2 infection. These data were generated using non-validated SARS-CoV-2 plaque-reduction neutralization assays with a reference strain and the Delta variant. The relative sensitivity of the two assays is not known.

This slide provides the results of the Delta variant neutralization analysis which shows that a 10-microgram primary series elicited PRNT neutralizing titers against both the reference strain and the Delta strain in participants 5 through 11 years of age with no evidence of SARS-CoV-2 infection up to one-month post-dose 2.

For your records, this slide provides the definitions of the protocol-defined COVID-19 and severe COVID-19 disease. COVID-19 was defined as the presence of at least one of the listed symptoms, including cough, shortness of breath, and chills, et cetera, meaning that only one symptom was needed to meet that definition and a confirmed SARS-CoV-2 PCR-positive test during or within four days before or after the symptomatic period.

In this descriptive analysis, vaccine efficacy against symptomatic COVID-19 after seven days post-dose 2 up to the data cutoff was 90.7 percent in participants without evidence of prior SARS-CoV-2 infection. A total of 3 cases of COVID-19 occurred in the vaccine group, 16 in the placebo group, with most cases occurring during July and August 2021 when the Delta variant was prevalent in the U.S.

At the time of the data cutoff, none of these vaccine cases met the criteria for severe COVID-19. All cases occurred in children without a prior history of COVID-19 infection. All cases of COVID-19 were confirmed by the central lab PCR at least seven days or more post-dose 2, and there were no cases of COVID in participants with a prior history of SARS-CoV-2 infection.

In the COVID-19 cases, vaccinated participants had less symptoms, one to three symptoms of COVID-19, but approximately one-third of the placebo recipients had more than five symptoms. No vaccinated participants had fever, while 10 of 16, or 65 percent,

of the placebo recipients had fever. Only one case occurred in a child with a predefined comorbidity, asthma.

All confirmed COVID-19 cases occurred in the U.S., except for one in Spain. No virus sequence analyses had been provided to the FDA to determine whether or not these cases were caused by the Delta variant or another variant. It's important to note that the study did not evaluate efficacy against asymptomatic disease or transmission, so we made no conclusions on that.

This slide provides a safety follow-up time for Cohorts 1 and 2 post-dose 2. What's important to note that, for Cohort 1, more than 95 percent had safety follow-up data for two to three months after dose 2.

For Cohort 2, 70 percent of the participants had safety follow-up data for at least two to three weeks after vaccination, which includes the timeframe in which most cases of myocarditis after vaccination have been observed. In both cohorts, over 3,000

participants were followed seven days or more.

Here we see the frequency of local reactions, including injection site pain, redness, and swelling within seven days after each dose, including the frequency of Grade 3 reactions. In general, local reactions occurred more frequently after dose 2.

Pain at the injection site was reported most commonly in almost 75 percent of participants for dose 1. The frequency of Grade 3 reactions after vaccination was low, seen in 0.3 percent of participants for pain at the injection site following either dose 1 or dose 2.

DR. ARNOLD MONTO: Dr. Ball, you're over time already.

DR. LESLIE BALL: Okay. We will go through this quickly. I think you've seen already the frequency of solicited adverse events within seven days after each dose. Systemic adverse events also generally occurred more commonly after dose 2. In the vaccine group, the most commonly observed systemic events were fatigue, headache, and muscle pain. For

both the systemic and local reactions, most were mild to moderate in severity.

This slide provides information on the onset of duration of solicited local and systemic reactions. The onset and duration for vaccine recipients were similar with both dose 1 and 2 with a median time of onset for local reactions of one day and for systemic reactions of two days. Both local and systemic reactions resolved within one to two days after onset.

The most common unsolicited adverse event was lymphadenopathy which was reported in less than one percent of the vaccine recipients. In both Cohort 1 and 2, there was only one participant that was withdrawn due to an AE, a child with fever to 40 degrees centigrade two days after dose 1 and a worsening of a preexisting neutropenia, the diagnosis of benign transient neutropenia.

FDA conducted standardized MedDRA Queries, or SMQs, to evaluate the constellation of unsolicited adverse events. The SMQs that occurred more commonly in the vaccine group than in the placebo, including

hypersensitivity reactions, consisting of primarily rash and dermatitis. Angioedema was included as facial swelling and urticaria cases. One participant, a 6-year-old vaccine recipient, reported Henoch-Schonlein purpura which was diagnosed 21 days after dose 1.

This was considered non-serious, and symptoms resolved after one to three days with no laboratory evaluations performed. All but one case event of rash with onset 12 days post-dose 2 were considered resolved at the time of data cutoff.

Chest pain was reported in six vaccine recipients and also six placebo recipients. All resolved without intervention and were considered noncardiac in origin.

In Cohorts 1 and 2, the SAEs occurred at a frequency of 0.1 percent and 0.2 percent, respectively, in the vaccine recipients, and 0.1 percent and 0 percent in placebo recipients, respectively.

SAEs included common events that occurred in this population, such as arthropod bite, knee infection, and fractures, and were considered unrelated

to vaccination. There were no reports of myocarditis or anaphylaxis and no participant deaths.

Here, I provide an overview of the pharmacovigilance, or PV, plan for the Pfizer-BioNTech COVID-19 vaccine. The plan includes monitoring for important identified risks, including anaphylaxis and myocarditis, and important potential risks, including vaccine-associated enhanced disease.

Under the PV plan, four post-authorization observational studies will be performed that includes the 5- through 11-year age group. Each of these studies involve monitoring for myocarditis and pericarditis.

MR. MICHAEL KAWCZYNSKI: All right, Dr. Ball. Because we didn't want to make sure we'd lose anything, we paused right there. Go ahead and continue.

DR. LESLIE BALL: Okay. This slide presents some key features for the two pediatric EUAs for the Pfizer-BioNTech COVID-19 vaccine, the EUA currently under consideration, 5 through 11 years of age, and the EUA issued in May for adolescents 12 through 15. The

proposed EUA, 5 through 11, involves a 10-microgram formulation while the 30-microgram formulation is authorized for use in adolescents 12 through 15 years of age. The clinical studies submitted to support the EUAs for both age groups included similar endpoints, similar immunobridging approaches, and similar descriptive efficacy analysis.

The safety database for vaccine recipients was approximately 3,000 in the 5- through 11-year age group and 1,100 in the 12- through 15-year age group. At the time of the data cutoff, the 5- through 11-year age group had over 1,400 participants with two months or more of safety data, and 12- to 15-year age group had 660 with 2 months or more of follow-up.

In summary, for immunogenicity and efficacy, the immunobridging success criteria were met for GMT and seroresponse rates at one-month post-dose 2. Descriptive immunogenicity analyses in a small subset of 34 vaccine recipients showed a 10-microgram primary series-elicited PRNT 50 percent neutralizing titers against both the reference and Delta strains.

Supplemental descriptive efficacy analysis showed vaccine efficacy against symptomatic COVID-19 after seven days post-dose 2 was 90.7 percent in participants without evidence of prior SARS-CoV-2 infection.

Regarding safety, local and systemic reactions were more common after dose 2. The most frequent reactions were injection site pain, fatigue, and headache.

Most frequently reported unsolicited AE was lymphadenopathy occurring in less than one percent of vaccine recipients. More vaccine recipients reported hypersensitivity-related events than placebo recipients. No anaphylaxis cases were reported.

Of the combined safety database of over 3,100 vaccine recipients, 4 SAEs reported; all were considered unrelated to vaccine. There were no reports of myocarditis or pericarditis.

In closing, I'd like to acknowledge the substantial contributions of my clinical colleagues, Dr. Maria Allenda, Lucille Lee, Rebecca Reindel, and

Susan Wollersheim, and statistical colleagues Dr. Yang and Lee Wong, as well as our many colleagues on the multidisciplinary CB team. That concludes my presentation.

FDA PRESENTATION: POST-MARKET ACTIVE SURVEILLANCE OF COVID-19 VACCINES IN THE PEDIATRIC POPULATION IN THE FDA BEST SYSTEM

DR. ARNOLD MONTO: Thank you, Dr. Ball. Now I turn the floor over to Dr. Wong who is going to talk about post-authorization evaluation briefly, I hope.

DR. HUI-LEE WONG: Indeed, it shall be brief but informative. Thank you, Dr. Monto.

Today on behalf of our multiple partners in the FDA BEST, we want to share one of the ways FDA actively monitors the post-market safety of COVID-19 vaccines in children.

The active surveillance system for biologics including COVID-19 vaccines is the FDA Biologics and Effectiveness Safety. That's the BEST system.

Illustrated on this slide, there are the multiple partners that we have. Our safety surveillance for COVID-19 vaccines, these yellow circles here is the large administrative claims databases where collectively they represent claims from each state in the United States.

In total here we see the pediatric population. This is roughly, approximately the annual enrollees per year breakdown by age. In total, that's around 20 million pediatric enrollees. That covers an estimated percentage of around 25 to 30 percent of the U.S. population.

While we generally use administrative claims databases because this is very helpful for potentially rare adverse events, BEST also has access to a number of electronic health records databases. Shown here on this slide are details of a pediatric EHR, or electronic health records, from eight pediatric hospitals.

I'll now move back to the database that we generally use in general for the safety surveillance,

and that is the claims database. I just shared with you four. Of these two of this year for the ages 12 to 17 Pfizer-BioNTech COVID-19 vaccine doses, we have around 1.2 million. These are currently being used for safety surveillance of COVID-19 vaccines.

FDA BEST monitors the safety of COVID-19 vaccines by monitoring the rate of outcomes. Here is a working list of 16 outcomes. None of these have been associated with COVID-19 vaccines based on preauthorization evidence. Working lists are added on as more information comes on.

What we do with that is that we monitor the rates of these outcomes close as they occur, hence they call it near real-time safety surveillance. For those above 65 years, it's every week. For those under 65 years, it's from 12 to 64 years.

This slide shows you one of our latest results that is for near real-time surveillance of Pfizer-BioNTech COVID-19 vaccines in 12 to 64 years. Here you can see that we did not detect any physical signals for elevated risk of rates of these outcomes, except for

anaphylaxis, but there's mitigation strategies currently in place.

While these are 12 to 64, for the pediatric population, we monitor right now to see whether any of the event occur, and then we do additional analysis. We call those observed versus expected analysis. I'll explain a little bit more of that, where we compare with the rate that's observed after vaccination with rates that is expected in the absence of vaccines, in this case, background rates. We will focus on certain age group of interest, for example where needed if it's male 12 to 15, for example.

In summary, FDA BEST is monitoring the safety of COVID-19 vaccines in near real-time surveillance. Specifically for pediatric population, we will conduct observed versus expected analysis for any of the subgroups of interest when events sufficiently accrue.

We have conducted these for myocarditis and pericarditis for males and female subgroups in pediatric populations. One of these input actually will be public input for the benefit-risk assessment

that our colleague, Dr. Hong Yang, will present.

I would like to thank the entire large, huge cadre of persons working with us, our FDA staff, for your dedication throughout weekends, throughout holidays, for our collaborators, all the BEST collaborators too numerous to be named here actually, for keeping pace with us as we provide timely and yet rigorous data in terms of COVID-19 vaccine surveillance. Thank you. This concludes my remarks.

FDA PRESENTATION: BENEFITS-RISKS OF PFIZER-BIONTECH COVID-19 VACCINE FOR AGES 5 TO 11 YEARS

DR. ARNOLD MONTO: Thank you, Dr. Wong. You were indeed brief. Dr. Hong Yang is our next speaker who will be talking about benefit-risk analysis. She's from the Office of Biostatistics and Epidemiology, CBER. Dr. Yang.

DR. HONG YANG: Hi. Thank you. My name is Hong Yang. I'm senior advisor for benefit-risk assessment, Office of Biostatistics and Epidemiology in

CBER.

Today, I'm presenting a benefit-risk assessment for use of Pfizer-BioNTech COVID-19 vaccine for age 5 to 11 years.

To authorize use of a drug or biologic product, FDA need to determine whether the benefit outweigh the risk. For COVID vaccine, the key benefits are preventing of COVID-19 cases, hospitalization, ICU stays and death due to COVID-19. The key risks are myocarditis, pericarditis cases attributable to vaccine or related hospitalization, ICU stays, and death.

Throughout the rest of the presentation, I will use myo cases to represent both myocarditis and pericarditis. FDA conducted analysis to assess the benefits and risks per one million individuals who received two dose of Pfizer vaccine. Analysis was conducted first by male, female, and both sex combined. For (inaudible) purpose, FDA's approach is purposefully conservative.

FDA assessed the benefit of vaccine within six months post second dose. This slide shows the model

assumption and input for Scenario 1 or we call base scenario.

Two general assumptions were made. First, duration of vaccine protection is six months post second dose of vaccine, efficacy remained constant. The second is incidence of COVID cases, hospitalizations, ICU stays, and death are stable over the period. To estimate the benefit of vaccine, we used the COVID incidence data available from COVID NET of the week of September 11, 2021. We took an average of four weeks prior to September 11 for incidence of hospitalization and historical average rate for ICU stays and death. We assumed vaccine efficacy 70 percent against cases and 80 percent against hospitalization.

This is of CDC vaccine effectiveness study which monitoring the Pfizer vaccine recipients age 20-to 64-years-old for both pre-Delta and Delta period. To estimate the risk, we used the myo incidence data age 12 to 15 years from OPTUM. That is the healthcare data, a part of FDA's Sentinel BEST system. We used

this 12- to 15-years data because the data for 5 to 11 years age is not available. The rate of hospitalization and ICU stays due to vaccine-related myocarditis cases were obtained from Vaccine Safety Datalink.

They found no death was determined to be associated with vaccine-related myo cases. The majority of the vaccine-related myo cases are in mild conditions, and they resolved in a short period of time. This base scenario is a temporary (inaudible) of our modeling. It does represent the most likely scenario. There are major uncertainty associated with model assumption and the incurred. On the next two slides, I will discuss the uncertainties and the alternative model scenario used to evaluate the impact of those uncertainties.

One of the key uncertainties is the future dynamic of the pandemic. The COVID-19 incidence has great influence on the benefit of the vaccine. The higher the incident, the greater the benefit, vice versa. We use the recent peak incidence and the lowest

incidence in Scenario 2 and 3 to represent the bound of future pandemic with a caveat that incidence may but are less likely (inaudible) response. Another issue is inconsistency in COVID death rate derived from CDC Data Tracker compared to COVID NET. We use Scenario 5 to (inaudible) the impact of these inconsistencies.

In the death scenario, we use vaccine efficacy of 70 percent against cases and 80 percent against hospitalization based on CDC Vaccine Effectiveness Study. Recently, a sponsor submitted a supportive efficacy analysis which suggests 90.7 percent efficacy against COVID-19 among age 5 to 11 years. We used this higher efficacy in Scenario 4. Last, there is great uncertainty on incidence of excess myo cases among the age 5 to 11 years. There are two layers of uncertainties. First, no data available for age 5 to 11 years old.

We used the rate for age 12 to 17 years. However, historical data on classical myo cases suggest that the risk among age 5 to 11 years may be lower than the age 12 to 17 years. In addition, the incidence

(inaudible) of proposed vaccine for 5 to 11 years of age is lower than the vaccine for 12 to 15 years for the use under the EUA.

The observed systemic reactogenicity in clinical trial is lower accordingly. There is speculation that the incidence of excess myocarditis cases may be lower in age 5 to 11 years. Second, both Vaccine Safety Datalink data and Vaccine Adverse Event Reporting System suggested a lower excess myocarditis case rate among (inaudible).

Even though we believe OPTUM data fit best for the purpose of this study, there may be uncertainty due to limited sample size and limitation of the healthcare data. Also, the case is not reviewed in depth, so that may cause the overestimate of the myocarditis case rate. We use Scenario 6 to represent a potential 50 percent lower incidence for excess myo case. Sorry. I forgot to advance slide.

Next, I will present the benefit-risk assessment results. Scenario 1, here I will remind you this is the key assumption and model input used in this

scenario, COVID-19 incidence at the week of September 11, 2021.

We used vaccine efficacy 70 percent against cases and 80 percent against hospitalization. The rate of excess myocarditis is coming from OPTUM's data for age 12 to 15 years old.

This bar chart from top down present model-perceived benefit-risk assessment for male age 5 to 11, 12 to 15, and 16 to 17 years. The vaccine has been authorized under EUA for later two age group. The benefit-risk of these two groups were for past year for comparison.

On the left side of each bar chart are four benefit endpoints. From bottom up, prevented COVID cases, hospitalization, ICU stays, and death.

On the right side of the bar chart are four risk endpoints. From bottom up, excess myo cases, hospitalization, ICU stays, and death. When we compare the benefit and risk side by side, we need to keep in mind that the clinical implication of hospitalization and ICU stays due to COVID-19 are very different from

those due to vaccine-related myocarditis. The former require much more extensive clinical care and later typically to monitor patients' condition as a precaution.

Looking at the chart on the top, for male age 5 to 11 years, model predicts vaccine prevent about 45,000 COVID cases, 203 hospitalization, 57 ICU stays, and 1 death among 1 million fully vaccinated individuals.

In the meantime, this vaccine may cause 179 excess myo cases, 98 hospitalizations and 57 ICU stays. The benefit appear to outweigh the risks. There're similar result for the other two age group.

This bar chart for female under base scenario. For all three age groups from top down, the benefits clearly outweigh the risk. The benefit-risk are clearly more favorable compared to the benefit-risk for male presented on the previous slide.

These are bar chart for male and female combined. Similarly, we can see for all age group the benefit clearly outweigh the risks.

Scenario 2 with peak incidence. On this slide, there are three bar chart, top down, for age 5 to 11 years, male, female, and male-female combined. For sake of time, from now on, I will focus on the result for 5 to 11 years old, male only. This is the group with the highest risk. The female and two sets combined always have more favorable benefit-risk compared to the male group. For Scenario 2 with peak incidence for age 5 to 11 years male, model predicts vaccine prevents about 54,000 COVID cases, 250 hospitalization, 82 ICU stays, and 1 death while vaccine may cause 179 excess myo cases, 98 hospitalizations, and 57 ICU stays. The benefit appears to outweigh the risk.

Scenario 3 with the lowest COVID-19 incidence. For male 5 to 10 years old, the chart on the top, the model predicts much lower benefit, which is prevention of 2,639 COVID cases, 21 hospitalizations, and 7 ICU stays. However, the vaccine may cause 179 excess myo cases, 98 related hospitalizations, and 57 related ICU stays. Where the benefit of vaccine outweighs the risk

under this scenario, this may require a (inaudible). Considering the clinical implications and the length of stay for COVID-19 versus myo-related hospitalization and ICU stays and the benefit of preventing COVID-19 (inaudible) morbidity. So overall, benefit of the vaccine may still outweigh the risk.

Scenario 4 with higher vaccine efficacy. For male 5 to 10 years, the model predicts vaccine will prevent about 58,000 COVID cases, 254 hospitalizations, 83 ICU stays, and 1 death, while cause 179 excess myo cases, 98 hospitalizations, and 57 ICU stays. The benefit appears to outweigh the risk.

Scenario 5 with the higher COVID death rate. For Scenario 5, the male 5 to 10 years, the model predicted prevention of about 45,000 COVID cases, 203 hospitalizations, 67 ICU stays, and 3 deaths. However, vaccine may cause 179 excess myo cases, 98 hospitalizations, and 57 ICU stays. So overall, benefit appear to outweigh the risk.

The last, Scenario 6, with 50 percent lower myocarditis case rate. For male 5 to 10 years, the

model predict about 45,000 COVID cases, 203 hospitalizations, 57 ICU stays, and 1 death. However, it may cause 89 excess myo cases, 49 hospitalizations, and 29 ICU stays. The benefit clearly outweigh the risks.

This is the results slide. The greatest uncertainty of this analysis is associated with the assumption that the pandemic remains stable over the next six months, which leads to great uncertainty on the prediction of vaccine benefit.

Vaccine efficacy may change due to emerging of new variants. Hospitalization and ICU stays from COVID-19 or vaccine-related myocarditis have bigger clinical implications in comparison (inaudible).

FDA's assessment is conservative. The benefit of reducing COVID-related multisystem inflammatory syndrome may not fully capture this by the full benefit endpoint used in this analysis. This benefit-risk assessment does not consider potential long-term benefits and risk. This benefit-risk assessment does not include secondary benefits and risks such as

prevention of disease transmission, in-person learning of the children, socioeconomic impact, and so on.

In conclusion, in the five out of six model scenarios, model predict favorable benefit-risk for the Pfizer vaccine. Under Scenario 3, the model predicts more excess than prevented hospitalizations and ICU stays in male and both sexes combined. However, considering the difference in the clinical implications and the length of the stay for hospitalization and ICU stays due to COVID-19 versus vaccine-related myo cases and the benefit of preventing COVID-19 with significant morbidity, the overall benefit of the vaccine may still outweigh the risk.

Finally, I would like to acknowledge the member of FDA benefit-risk assessment team, Dr. Patrick Funk; Osman Yogurtcu for their excellent contributions to the benefit-risk modeling; and to Dr. Rich Forshee, his leadership. We thank CDC Vaccine Task Force for sharing initial benefit-risk assessment model also the data on COVID-19 pandemic. We thank Acumen and OPTUM team for providing myocarditis incidence data. We also

thank many of our FDA colleagues for their input through their analysis.

DR. ARNOLD MONTO: Thank you, Dr. Yang. We're running a bit late, so that we are not going to be able to entertain questions now. What I think we will do when we resume after lunch and the open public hearing is to ask Dr. Yang to put up her conclusion slide again, and then we will have our question and answer period from the members because this is an important presentation. We really need time to discuss the presentation before we go into our general question and answer period. So break now until the open public hearings at 1:00. Then we resume questions and answers at 2:10, I believe, all Eastern Time.

[LUNCH BREAK]

OPENING PUBLIC HEARING

MR. MICHAEL KAWCZYNSKI: All right. Good afternoon and welcome back from that lunch break to the

170th VRBPAC meeting. We are now going to go into our afternoon portion of today's activities. So, Dr. Arnold Monto, are you there?

DR. ARNOLD MONTO: I am. And I'd like to welcome everybody to the open public hearing session. Please note that both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee 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 speakers, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with the product, the sponsor, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of expenses in connection with your participation in this meeting. Likewise, FDA encourages you, at the beginning of your

statement, to advise the Committee if you do not have any such financial relationship.

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

DR. PRABHAKARA ATREYA: Thank you, Dr. Monto. Before I begin calling on the registered speakers, I would like to add the following guidance. FDA encourages participation from all public stakeholders in its decision-making process. Every Advisory Committee meeting includes an open public hearing session, OPH session, during which interested persons may present relevant information or views. Participants during the OPH session are not FDA employees or members of this Advisory Committee.

FDA recognizes that the speakers may present a range of viewpoints. The statements made during this open public hearing session reflect the viewpoints of the individual speakers or their organization and are not meant to indicate the agency's agreement with the

statements made. With this guidance, I would like to move forward with the registered speakers. The first speaker is Dr. David Burger.

MR. MICHAEL KAWCZYNSKI: All right, Dr. Burger. Take it away.

DR. DAVID BURGER: My name is Dr. David Burger. I have no financial conflicts of interest.

Slide number 2. I am a board-certified pediatrician with more than 25 years of clinical experience. I practice primary care with a focus on optimizing nutrition and lifestyle. I offer vaccine consultations for all ages.

Slide 3. I serve a diverse patient population and am hearing more COVID-19 vaccine hesitancy for the 5 to 11 age group than I did for adolescents. People with vaccine questions often look to me as a trusted source of information. I explain that for most people immunity will develop following vaccination or natural infection, but the strength and duration of immunity varies. I suggest that they make a benefit versus risk list for both getting the vaccine as well as catching

the virus. I am glad I can share the Pfizer briefing data and let parents know that the safety and efficacy studies will be ongoing for two years.

Slide 4. My approach to vaccine hesitancy is, rather than expel families from my practice as many pediatricians do, I find that having patience, acknowledging concerns, and educating in a non-threatening way allows people to make the best choices for themselves, including deciding whether to vaccinate their children. A number of them eventually choose to vaccinate; some do not.

Slide 5. According to the Pfizer data, 3,750 children were given 10-microgram doses of the vaccine, 750 received a placebo. The antibody response using the lower dose was similar to that found in older children who were given 30 micrograms. This is promising data. If authorized, I am glad parents will have the choice to give this lower dose product.

Slide 6. Parents are asking many questions, including whether the vaccine will likely result in a significant reduction of pediatric hospitalization or

death especially since these outcomes are already rare in young children. The Pfizer data shows a 90 percent reduction of symptomatic disease among this population.

They ask if a reduction of pediatric long-haul incidents can be expected. We have seen cases of long-haul COVID in our practice but not among the young children. Parents want to know if the vaccine is expected to reduce family and community spread. I explain that the more people who have immunity, the more protected those are around them.

Slide 7. Parents are asking if the sample size was adequate. Assuming an approximate number of children at each age, the study included an estimated 1,600 children vaccinated age 5 to 7 and 1,100 children in the 8 to 9 and 10 to 11 age groups.

Slide 8. Parents want to know about myocarditis and if there could be side effects specific to this age group that are not seen in older people. They ask how to optimize nutrition and moderate inflammation. I explain that having good vitamin D and zinc levels, adequate sleep, and physical fitness are

all beneficial.

Slide 9. It's important to recognize that parents make decisions that they think are best for their children. Many will vaccinate right away, some will wait, and some will choose not to vaccinate. Even vaccinated parents may be uncomfortable vaccinating their young children, especially at the beginning. I find most people with hesitancy about the COVID vaccines are not who are often labeled anti-vaxxers. I would like to take this opportunity to call for understanding, civility, and respect. No one benefits if we judge and ridicule each other.

Slide 10. Thank you for allowing me this opportunity to present to you.

DR. PRABHAKARA ATREYA: Thank you, Dr. Burger. The next speaker is Steve Kirsch.

MR. STEVE KIRSCH: Hi, I'm Steve Kirsch, Executive Director of the COVID-19 Early Treatment Fund. I have no conflicts of interest.

Slide 2. Why are kids dropping like flies right after getting vaccinated? If they didn't die

from the vaccine, then what killed these kids?

Next slide. How can a healthy 16-year-old boy die in the middle of a Zoom math class? He was fine 20 minutes before he died.

Next slide. The doctor's found nothing, what did the CDC find?

Next slide. Why did this 15-year-old die in his sleep just two days after getting vaccinated?

Slide number 6. How did you miss all of these safety signals?

Slide number 7. If the vaccines are so safe, how come Taiwan officially admits that the vaccines killed more people than the virus?

Slide 8. Do you find this recent U.K. headline troubling?

Slide 9. How are Germany and Norway both able to determine causality in sample sizes of 100 or less, but the CDC can't determine causality in over 16,000 deaths it has investigated?

Slide 10. How come deaths in Israel go up when vaccinations go up and go down when vaccinations

go down?

Slide 11. What is the VAERS under-reporting factors? How can you do a risk-benefit analysis if you don't know the URF? This is extremely, extremely important. You've been assuming it's been one, it is not one.

Slide 12. Using a URF of 41 which is calculated using the CDC methodology, we find over 300,000 excess deaths in VAERS. If the vaccine didn't kill these people, then what did?

Slide number 13. Is there any stopping condition to these experiments? How many Americans have to die before you pull the plug? How many kids have to die before you yell, stop?

Slide 14. Why are there no autopsies for deaths after vaccination?

Slide 15. Why didn't the highly unusual causes of deaths in these kids raise any red flags in the CDC 12 to 17 safety study? They didn't even comment, they said just move on, nothing to see here.

Slide 16. How many months do troponin levels

stay elevated after vaccination?

Slide 17. Of the over nearly 140,000 comments have been posted against the vaccines in kids, I found only one comment in favor. How many did you find?

Slide 18. Did you ever read the Kostoff paper? It says that five times as likely to die from the vaccine as from COVID. And it's even worse if you're younger.

Slide 19. Why was this paper removed over the objections of the editors?

Slide 20. They found 19 times the expected number of myocarditis cases and a 5-fold increase on dose 2.

Slide 22. Is this what you mean by slightly elevated risk?

And let's skip to Slide 26. How can a kid who was in the Pfizer 12- to 15-year-old trial be paralyzed and not have that reported to the FDA? How can you approve a vaccine for under 12 when you haven't investigated this study?

Let's skip to the end here, Slide number 30

which is the complete list of my questions are posted on "TrialSiteNews" today. Just search for VRBPAC.

There are too many unanswered questions for you to approve the vaccine for 5- to 11-year-olds. Thank you.

DR. PRABHAKARA ATREYA: Thank you. The next speaker is Dr. Andrea Kline-Tilford.

DR. ANDREA KLINE-TILFORD: Greetings. I'm Andrea Kline-Tilford. I have no conflicts of interest.

I'm a pediatric nurse practitioner and president of the National Association of Pediatric Nurse Practitioners, a professional organization representing more than 8,000 pediatric-focused advanced practice registered nurses. We support the timely and complete immunization of all infants, children, and adults in an attempt to maximize the health and well-being of all people. The last 20 months have brought immense strain to the world, including our nation's more than 20 million children 5 to 11 years of age. Our children have been pivoting in all areas of life.

Slide 2. The strain has been immense and has

resulted in physical and mental health challenges that will undoubtedly have lasting impacts on social, emotional, and mental health. In a poll conducted by researchers in Chicago, 71 percent of parents or caregivers believe the pandemic impacted their child's mental health.

Pediatric nurse practitioners are on the front line in primary and acute settings encountering these challenges in our children each and every day. There has been an alarming increase in child and adolescent anxiety, depression, and suicide. According to the CDC, mental health-related emergency department visits by adolescents increased by 31 percent in 2020. And at one point during the pandemic, emergency department visits for suspected suicide attempts in girls was up 51 percent from 2019.

Additionally, eating disorders, sometimes deadly, increased 62 percent during the pandemic and an estimated 140,000 children have lost parents and caregivers due to COVID-19. Let's not forget the physical ramifications of COVID-19. Children can and

do suffer acute illness, multi-system inflammatory syndrome, and long-haul physical symptoms. Over the last several months the number of COVID cases in children has substantially increased.

Data from October of 2021 reveals more than 630 pediatric deaths from COVID-19 and at least 46 pediatric deaths associated with MIS-C. Children have paid a significant toll, and we have the ability to alter this trajectory. Right now, we rely on masking, physical distancing, hand hygiene, and surrounding children with adolescents and adults that are vaccinated. Without other options, these strategies were acceptable but are not a solution and leave a tremendous gap in protection for our children.

Slide 3. NAPNAP urges the FDA to authorize the Pfizer-BioNTech COVID-19 vaccine for children 5 to 11 years and supports widespread equitable rollout to every eligible child in the U.S. using all possible vaccination sites, including primary care offices, schools, heath centers, pharmacies, popup sites, and mobile units. COVID-19 vaccination is safe and

effective, and, with the adjusted dosing for children 5 to 11, we can protect our school-aged children immediately and further shield them from short and long-term physical and mental health consequences.

Let's use the newly provided data on the Pfizer vaccine to deliver comprehensive, equitable immunization to all children 5 to 11 years of age. Thank you for this time to share the views of the National Association of Pediatric Nurse Practitioners and my own views as a mother of two children under 12 years of age.

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

DR. JESSICA ROSE: My name is Dr. Jessica Rose, and I'm a virtual immunologist and computational biologist. I have no conflicts of interest.

Note number 1. Emergency use authorization of biological agents requires the existence of an emergency and the non-existence of alternate treatments. There is no emergency, and COVID-19 is exceedingly treatable.

Note number 2. Individuals with resolved COVID-19 infection are potentially pathogenically primed for subsequent CH2 immunopathology. If injected with a targeted immune stimulant in the form of a host-run spike protein manufacturing system, this could trigger subsequent inflammation, immune complex formation, and over-activation of the complement system leading to myocarditis and other immunopathologies that are in fact being prolifically reported to VAERS. VAERS reports must include prior COVID-19 infection status in order to make it possible to assess the potential relationship between immuno-related pathologies including myocarditis and the injections.

Slide 1. On the left is a bar plot from a recently accepted for publication peer-reviewed paper showing the absolute numbers of VAERS reports of myocarditis according to age group. Myocarditis rates were significantly higher and used age 13 to 23. Within eight weeks of the COVID-19 roll out for ages 12- to 15-year-olds, 19 times the expected number of myocarditis cases were reported over background rates

for this age group. In an act of censorship, this paper was temporarily removed and has now been killed without criticism of the work.

Considering the relevance of the confines of this paper to many, it seems not only strange but irresponsible to censor this paper at this point in time. The paper is being relied upon by many for the information therein, and you and the public at large deserve an opportunity to read it.

Slide 2. On the left is a bar plot showing myocarditis reports from the VAERS domestic datasets according to age and dose. The data is skewed in a statistically significant way towards children.

The reporting rate for boys aged 15 years is 6-fold higher for the second dose, which makes it plausible that the products are causing the adverse events and subsequent reporting. On the right is a similar bar plot according to age and gender. Of the reports, 80 percent of the gender classification was male. And in general, 70 percent of all VAERS reports are made by females, so this statistic is particularly

telling. What will happen in children ages 5 through 11?

Slide 3. Tens of thousands of reports have been reported to VAERS for children aged 0 through 18. In this age group, 60 children have died, 23 of them were less than 2 years old. Of the metric host listed, it is disturbing to note that products administered to patients of inappropriate age was filed 5,510 in this age group. This means that two children were inappropriately injected, presumably by a trained medical professional, and subsequently died.

Slide 4. This is a table showing several examples of VAERS reports for children between the ages of 5 and 11 who died. They died within zero, five, and an unknown number of days following the injection. The 11-year-old shown here was injected despite being too young. This is malfeasance. I implore you all to empathetically cast your votes using both your hearts and your minds. Thank you very much for this opportunity to speak.

DR. PRABHAKARA ATREYA: The next speaker is

Josh Guetzkow.

DR. JOSH GUETZKOW: My name's Josh Guetzkow. I'm a senior lecturer at the Hebrew University and have no conflicts.

Expanding the EUA to children is unnecessary, premature, and will do more harm than good.

Slide 2. There is no emergency for children, especially healthy ones whose risk of severe illness or death is almost nil. Kids with preexisting conditions and prior COVID infections were not included in Pfizer's study so including them in the EUA is negligence.

Slide 3. Correction, the 2268 number is for all subjects. Pfizer's trial is woefully underpowered to detect specific safety concerns such as myocarditis, just like the adolescent study was. And, if they weren't able to detect an unexpected safety concern there, they wouldn't be able to here. In Pfizer's study, only 0.5 percent of controls were dropped due to important protocol violations versus 3 percent in the treatment group. The odds of that happening by chance

are one in 10,000. This deviation is poorly explained with no (audio skip) wait.

Slide four. From CDC reports, we can expect that for every 18 child hospitalizations prevented at least 43 will end up in the hospital for all causes following vaccination. FDA's risk-benefit analysis only counts myocarditis hospitalization. Why ignore the V-Safe data? And shouldn't FDA verify Pfizer's efficacy and immunobridging analyses first?

Slide 5. VAERS shows alarming safety signals which we have shown cannot be attributed to increased vaccinations, stimulated reporting, or COVID infections.

Slide 6. We calculated the ratio of adverse events reported per million Pfizer vaccinations to reports per million flu vaccinations among teenagers to see what to expect in children. Serious events are reported 61 times more often for Pfizer, deaths 47 times, and life-threatening conditions 49 times.

Slide 7. Here are the Pfizer flu reporting ratios for some adverse event categories. Look at the

box on the left. What are we doing to their reproductive organs? How can you expect young children to take these risks to protect adults?

Look at myocardial disorders on the right and ask yourself why Pfizer's briefing document didn't mention their child sub-study on troponin levels. You should demand to see those results.

Slide 8. There are over 900 types of adverse events reported in teens from Pfizer vaccination that has never been reported for flu vaccines including 11 cases of MIS-C with no COVID infection. And that's before correcting for under-reporting. If you were hoping to prevent MIS-C, time to reconsider.

Slide 9. The fact is, your approval today means mandates tomorrow for healthy children who don't need it and for those who weren't studied. If you have even the slightest doubt about safety, you must vote against forcing these and unknown long-term risks on young children. So, in the name of millions of parents around the world, I implore you, hold the line. You won't be able to say you didn't know. Thank you.

DR. PRABHAKARA ATREYA: Thank you. The next speaker is Ms. Shoshana Fishbein.

MS. SHOSHANA FISHBEIN: Hi, this is Shoshana Fishbein. I have no conflicts of interest. Next slide, please.

Thank you to VRBPAC for all your hard work during the COVID-19 pandemic and also every year to ensure that our vaccines are safe and effective. It's fitting that I'm speaking today on behalf of Families Fighting Flu as you discuss vaccines for children. Our organization was founded when all children six months and older were not recommended to receive annual flu vaccines.

The founders of our organization are parents who lost healthy children to what they thought was just the flu. I'm here today to thank you for your hard work in ensuring children have access to safe and effective vaccines because our organization uses stories to show how vaccines can save lives.

Slide 3, please. We want to recognize the important work VRBPAC does every single year to make

recommendations about flu vaccine formulations. Although flu vaccines are not perfect, this Committee helps to ensure that the supply in America matches the strains most likely to circulate. Our stories are a cautionary tale of what happens when people do not take the flu seriously, and we've seen many parallels with COVID-19 and in children. We thank you for this important work that often goes unnoticed.

Lastly, we want to acknowledge the work that went into the last pandemic, H1N1, in formulating pandemic vaccines over a decade ago. Many of our stories are people who were hospitalized, on life support, or died from H1N1 flu, many of whom were children. And we know it’s important that COVID-19 vaccines are safe and effective for children 5 to 11 years old because children can and do spread COVID-19 and flu. The work that VRBPAC does is meaningful and necessary. Families Fighting Flu is just one of many examples of why prioritizing science and evidence-based practices is literally lifesaving. Thank you for your time and commitment to science.

DR. PRABHAKARA ATREYA: Thank you. The next speaker is Dr. Robert Edmonds.

DR. ROBERT EDMONDS: Dear Committee, I have no financial conflicts of interest to disclose.

Previously, I have reviewed the latest statistics of tinnitus with the Johnson and Johnson trial data as seen on the slide. While my main goal is simply to encourage early and appropriate treatment for this rare event and support continued COVID vaccination, I have also encouraged investigations into this matter because I have hope that there would eventually be study into the process that results in this condition.

Why? Because in early January, I got my first shot from a different vaccine and yes, a different platform, Moderna. Two to three weeks later, I developed tinnitus on the right side. I then received a second dose in early February. As with what happens to many who develop tinnitus after dose 1, I then worsened. The tone became louder, and I developed near-constant headaches, right side facial pressure,

numbness, paresthesia.

A few days after my second dose, my wife then received her first dose of Moderna. By early March, my wife received a second dose, but she then too developed tinnitus about a week later as well. While my other symptoms later resolved, both my wife and I continue to experience constant tinnitus. At the time of onset, we had no close contact and I later had a negative nucleocapsid test. I have also had normal scans and two normal hearing tests, something that appears unique but common to many with this adverse event.

Because of the staggered vaccination timing for us as a couple, but with symptom onset still coincidental with vaccination, it is hard to shake that this is not somehow a related difficult to detect, low-frequency adverse event despite not appearing in the trial data. Something even my providers work under the assumption of as described in their notes.

It leaves my wife and I in a challenging position. For one, is there some shared environmental exposure that increases the correlated risk to our

young daughter for experiencing this event in the future? Something I would never have dreamed of worrying about prior to this.

I know tinnitus is not considered serious, but this may be a permanent, lifelong condition. Also, it has led some who have developed tinnitus after COVID vaccination to thoughts of suicide due to the severity of the constant sound. I can also say that one individual, Dr. Timothy Boreing, completed suicide after battling tinnitus for seven months after a COVID vaccination. His daughter gave me permission to mention his struggle here today.

As I have mentioned in other comments, severity needs to be considered when determining a background rate of tinnitus to compare against. In Phoenix, ABC 15 ran a story discussing how there are 10,000 reports mentioning tinnitus in VAERS. The story highlighted me and two others that developed tinnitus. One, a member who once sat on this very committee, a little detail not widely known.

All three of us are a part of a tinnitus

adverse event pair. I know of many other tinnitus pairs not in the story as well, another unique curiosity that's gone unstudied. I know we are a small number in a sea of misery in this pandemic, but we rolled up our sleeves, defended our communities, and now we are asking for study into this issue. Thank you for this time.

DR. PRABHAKARA ATREYA: Thank you, Dr. Edmond. The next speaker is Dr. Beatrice Setnik.

DR. BEATRICE SETNIK: Good afternoon. My name is Beatrice Setnik. I'm a clinical pharmacologist and consultant to various pharmaceutical and biotech companies.

Slide 1 shows the total number of daily COVID cases and the current downward trajectory. Pfizer stated that most of the COVID cases observed in their study were during the July to August period, a time when the Delta variant was predominant and now makes up more than 99 percent of the tested strains. Despite this, the immunogenicity of the vaccine against the Delta strain was only tested in 38 children, using a

non-validated assay as an exploratory measure.

To date, Pfizer has not disclosed any biodistribution data for this vaccine. There is evidence that biodistribution and mRNA expression in these vaccine technologies are not limited to localization at the site of injection and may potentially cause safety implications for other organs and tissues.

On slide 2, the figure shows the number of COVID cases stratified by age group. COVID cases among 5- to 11-year-olds represent 5.3 percent of all COVID cases.

Five- to 11-year-olds have one of the lowest COVID case percentages in relation to their percentage in the U.S. population despite not having current EUA access to the vaccine. Furthermore, the 0- to 11-year-olds consistently have the lowest percent emergency department visits with diagnosed COVID.

On the next slide, Slide 3, COVID-19 deaths are reported by age group. Fortunately, there were few deaths reported for 0- to 17-year-olds. When we

examined the age groups 5 to 11 years, 156 deaths occurred, which represent 0.03 percent of the total COVID deaths.

The majority of COVID deaths were attributed to other comorbidities in the presence of COVID. COVID deaths in 5- to 11-year-olds were at 0.008 percent by total numbers of COVID cases. When deaths were examined on the whole population of 0- to 17-year-olds, these compromised -- and please note the correction on the slide, the correct number is 0.014 percent deaths relative to the total COVID-19 cases reported in this age group. The overwhelmingly high likelihood of survival rate up to 99.99 percent in children is not a justification for emergency use.

We can skip to Slide 5 which shows the adverse events reported to the VAERS database following exposure to the Pfizer vaccine with 25 deaths reported for the 6- to 17-year-old age group, and 245 life-threatening events. VAERS is notoriously under-reported. In Canada, 206 reports of Bell’s Palsy recently warranted an update to the COMIRNATY Product

Monograph. Canada has one-tenth of the U.S. population. In addition, there have been increasing reports of menstrual irregularities following COVID vaccination, to the point that the NICHD recently awarded $1.67 million in research funds to further explore this.

Yet this does not even appear as an adverse event of special interest in this study. What impact does this vaccine have on our vulnerable pre-pubescent and developing girls? What increased risks will occur in children with the clearly short-lived and waning effects of the vaccine that will require an unknown number of booster shots in the future? The risk-benefit analysis presented today does not account for any of this. We know the risks of myocarditis and pericarditis are a real risk, particularly for young boys.

Slide 6 shows the post-approval requirements that the FDA mandated to Pfizer on August 23rd. This demonstrates that many years of additional studies are required to establish the safety and efficacy of

COMIRNATY in both children and adults. Long-term complications of myocarditis after vaccination will not have final reports until May of 2027.

On the next slide, Slide 7, the guidelines for emergency use authorization clearly state that the known and potential benefits must outweigh the known and potential risks of the vaccine. Pfizer makes assumptions that vaccinations may cause a substantial reduction in virus transmission. However, the CDC citation Pfizer provided clearly states that more studies are needed, and that transmission does in fact occur with the vaccinated.

Finally, on Slide 8, Health Canada is reporting a high number of reported rates of serious adverse events following administration of the Pfizer COMIRNATY vaccine with a majority appearing after the first dose. Assuming drug safety has had devastating consequences, Thalidomide being one such example that caused deformities in newborn children.

In the 1990s, the FDA assumed that oxycontin had less abuse potential compared to other opioids,

making a false claim that helped fuel the opioid epidemic that still ravages our children in communities to this day.

Please do not assume that this vaccine is safe in our children until all data, including long-term data, has been carefully evaluated. Thank you.

DR. PRABHAKARA ATREYA: Thank you, Dr. Setnik. The next speaker is Ms. Amy Alvo.

MS. AMY ALVO: Hello, my name is Amy Alvo. I have no conflicts of interest.

I am here on behalf of my daughter, Abigail Alvo. At age 17, she was a perfectly healthy teenager, played softball since she was 5 years old, and was cheer captain of her high school cheer team. Thinking I was protecting my daughter as she would be traveling for summer vacation, I allowed her to receive the vaccine. I couldn't be more wrong.

On March 31, 2021, Abby was given the first dose of the Pfizer vaccine. This was the only vaccine approved for her age group. After the vaccine was administered, Abby felt faint. She slept the rest of

the day. The following morning, April 1st, Abby woke up not feeling well but she insisted on going to work.

A few hours into her shift, we received a phone call from HR that Abby had fainted and was shaking uncontrollably to the point she couldn't walk. Abby was taken to the ER and rushed in. They immediately started running tests. She was given an IV with a cocktail of drugs until she was heavily sedated. She was having a neurological reaction and no one had answers.

Her final diagnosis was an adverse effect of the coronavirus COVID-19 vaccine. All of our questions and concerns were met with uncertainty. The doctors did not know. They couldn't answer any of our questions. Could Abby's injuries get better? Could they get worse as she ages? Is this the early stages of Parkinson's? No one knows. There are no long-term studies available. Abby is the study and collateral damage. All of our children will be the study.

Within a few weeks of Abby's hospital discharge, we received a check from the hospital paying

us back for our copay from our ER visit. Never have I received money back from a hospital.

It has almost been seven months since Abby received the vaccine. Her right arm continues to shake uncontrollably. California is now mandating the vaccine, and Abby's school is requiring her to be fully vaccinated by November. We thought we would easily get a medical exemption due to having a documented adverse reaction to the Pfizer vaccine. We requested the medical exemption. It was denied not once, but twice. We were told there are two other vaccines that Abby could try.

I am asking all of you today. Do not allow our children to be experiments. Children are at extremely low risk of having severe reactions from COVID. The Pfizer vaccine has no health benefit to this age group. In fact, the vaccine causes catastrophic side effects, particularly heart inflammation and neurological damage. The long-term studies are not there. It is too soon. We are causing more harm to our children.

As parents and lawmakers, it is our job and duty to protect our children. I failed my daughter in allowing her to get this vaccine. Now she has neurological damage.

Don't allow the same thing to happen to other children. Please do not pass the emergency use authorization of Pfizer's vaccines for kids 5 to 11. Thank you.

DR. PRABHAKARA ATREYA: Thank you, Ms. Alvo. The next speaker is Ms. Belinda Macauley.

MS. BELINDA MACAULEY: Good morning from Thousand Oaks, California. My name is Belinda Macauley. I'm an attorney and a nonprofit executive but, for today's purposes, a parent. I have no conflicts of interest.

I'm here to speak in strong support of approval of the COVID vaccine for ages 5 to 11. As a family who has taken COVID seriously and tried to sensibly manage risk, the expansion of the vaccine to younger kids represents a welcome and critical next step in keeping ourselves and our community safer.

My husband and I have an 8-year-old daughter. We were fortunate to have the resources to keep her remote for last school year as cases surged in our region. We sent her back in person this year for third grade, and she had a COVID positive classmate on the first and second days of school. Fortunately, no other kids in her small classroom became ill, thanks in part, I'm sure, to masks.

But the risk of exposure remains, including from unvaccinated volunteers that our state and school board allow in classrooms. In fact, I received a notice of another case on campus last night as I was finalizing these remarks. I am aware that my healthy daughter's odds of becoming very ill with COVID-19 are quite low. Our concerns are primarily broader.

What if she inadvertently gets someone more vulnerable sick? We have friends and family members who are high risk. My mother is in hospice nearby, so staying COVID negative so that we can visit her in the care facility is extremely important to us. And, if COVID continues to widely circulate, all of us are

impacted. We haven't taken our daughter to eat inside at a restaurant, to the movies, or on a plane since COVID began. She wears KN95 masks anytime she's indoors in public.

I share this not to complain but to say that we are doing what we can. But we welcome the additional protection of vaccines to help her and other kids return to more of a normal life. If the data shows the vaccine is safe and helps prevent transmission and severe disease, my family is enthusiastically in favor of our prompt approval and our daughter will get it the first day it's authorized.

My friends with young kids look forward to your approval of this vaccine and tellingly, those who have experienced COVID-19 and its effects on a daily basis are the most supportive. One friend said, "My husband is an ER physician, and I am immune-compromised. Needless to say, we are eagerly awaiting the vaccine approval for our 5-year-old daughter and will be first in line once it is approved."

A friend who teaches elementary school shared,

"Teachers are on the front line of keeping our children and their families safe in their school environment. The emotional stress of thinking that you are the one responsible for the health and safety of families is overwhelming. Knowing that these children could have protections outside" (audio skip) "teach parents and students."

When I was growing up, my mom had a framed newspaper clipping of my grandfather from the 1950s. He was a doctor and administering polio vaccines. There was a line extending beyond the picture of kids waiting to be vaccinated.

I regret that the understanding of vaccine necessity is not as broad as it was then. Those who believe in science and public health should have the opportunity to give our kids a safe and effective vaccine that helps protect them, their schools, and our larger communities.

I hope this Committee will provide that chance soon.

DR. PRABHAKARA ATREYA: Thank you. The next

speaker is Ms. Kim Witczak.

MS. KIM WITCZAK: Good afternoon. My name is Kim Witczak, and I am speaking on behalf of Woody Matters, a drug safety organization started after the death of my husband due to an undisclosed side effect of antidepressants. We represent the voice of families who live every day with the consequences of the current drug safety system. You face a tough decision today, whether or not you will authorize Pfizer's EUA application for use in children 5 to 11 years old.

The outcome has the potential to force mandate this experimental vaccine into the bodies of tens of millions of children with limited evidence showing benefit outweighs the harm. The current VAERS data shows that COVID vaccines pose a significant risk to teens and young adults with issues of myocarditis, blood clots, and other neurological injuries. This is in addition to all the unknown risks which will only be discovered over time and in much larger numbers than the 1,000 children in Pfizer's two-month trial.

Is there really an emergency with this age

group or is it being driven by a larger political agenda? The Biden administration has already secured millions of doses and has a distribution strategy ready to roll. California Governor Newsome and other governors have already indicated the intention to mandate all school children K through 12 following FDA approval. It must be exceedingly difficult to vote your conscience when it seems that all the decisions have already been made for you.

Are you aware that there are almost 140,000 comments from people across the country in the Federal Register for today's meeting? As a member of another FDA advisory committee, I have never seen this much engagement from the public. I sure hope this Committee, the FDA, and the Biden administration takes time to read all the comments before making the decision.

We live in a polarized society today. There are two segments of American people: one that eagerly awaits FDA authorization, and a large segment of the American public that is not quite ready to inject their

children with an experimental product and certainly don't want to be forced in order to go to school or live-in society.

Let's be honest, an EUA will almost certainly result in mandates across the country, regardless of what the law says. One idea that was floated back in December 2020 at the first EUA hearing was to consider the expanded access program. This way it gives parents who want the vaccine for their children to get it now, but, for those who don't, they will not be mandated. Everyone wins. Expanded access will allow parents to make the best decision for their children instead of taking that choice away through mandates.

After all, it will be the parents who will have to live with the results of this decision, not government officials or schools if something bad happens to their child. And remember, even without an expanded access program this particular Pfizer vaccine is fully approved. So parents can already get this vaccine off-label from their doctor. An EUA is not necessary.

In closing, all eyes are on you. If there is any, any hesitation in a Committee member's mind about this vote then, at the very least, you should state for the record that you do not believe an EUA should lead to mandates.

Our kids are not for sale. Leave parenting to parents. Thank you for your consideration.

DR. PRABHAKARA ATREYA: Thank you for the comment. Next speaker is Luke Yamaguchi.

MR. LUKE YAMAGUCHI: Hello, my name is Luke Yamaguchi. I have no financial conflicts of interest to disclose.

From March through October of last year, children 5 to 14 years old had a one in a million chance of dying with COVID-19 in the United States. For perspective, children in this age group were about ten times more likely to die from suicide than from COVID-19.

A recent article in the *New York Times* cited data showing that unvaccinated 5- to 11-year-old children are actually at less risk of hospitalization

from COVID-19 than fully vaccinated older adults. For children 5 to 11 years old, the weekly rate of COVID-19 associated hospitalization has ranged from 0 to a peak of 1.1 per 100,000 population.

Regarding herd immunity, the state of Vermont, despite having the highest COVID-19 vaccination rate in the country is currently experiencing the highest number of active COVID-19 cases they have ever had during any point in the pandemic. Similarly, the country of Singapore, with 84 percent of their population fully vaccinated is now experiencing their largest wave of COVID-19 cases and deaths since the beginning of the pandemic.

With this in mind, I want to mention three factors that must be taken into account when making a risk-benefit analysis for COVID-19 vaccines in low-risk pediatric populations. The first one I want to make is that pediatric hospitalization rates are inflated by the detection of mild or asymptomatic infection due to universal COVID-19 testing procedures in hospitals. One study out of Stanford found that 45 percent of

pediatric COVID-19 hospital admissions were not caused by SARS CoV-2 infection. And so this must be accounted for in your risk-benefit analysis.

Additionally, the risk of recommending COVID-19 vaccines to children who already have natural immunity against COVID must be taken into account. Current estimates would suggest that almost 50 percent of children have now recovered from COVID-19 and acquired natural immunity. The research is abundantly clear now that natural immunity to COVID-19 is vastly superior to vaccine-induced immunity because COVID-19 vaccine-induced immunity rapidly wanes over time and requires future booster doses, each of which carry their own risk.

Furthermore, there is an additional risk with vaccinating people who have previously had COVID-19. Data out of the U.K. shows that prior COVID-19 infection is associated with increased risk of adverse events from Pfizer's COVID-19 vaccine with young individuals more likely to report adverse events. So for about half the children in the United States who

have likely already acquired natural immunity, the risks of COVID-19 vaccination almost certainly outweigh any possible benefit. And this needs to be accounted for in your risk-benefit analysis.

The last thing I'll say is that it's possible that people who get a COVID-19 vaccine will need to get another booster dose every six months, potentially for the rest of their life. And with every additional booster dose, there will be the risk of myocarditis along with the risk of other adverse events. You can't just look at a six-month risk-benefit analysis and say that it's all good. You have to look at the long-term risks versus benefits taking into consideration that natural immunity is broad, robust, and long-lasting, and vaccine-induced immunity is not.

And so I urge the Committee to exercise the precautionary principle and withhold the EUA of Pfizer's COVID-19 vaccine for children 5 to 11 years of age. Thank you very much for your time and consideration.

DR. PRABHAKARA ATREYA: Thank you. The next

speaker is Dr. Brian Dressen.

DR. BRIAN DRESSEN: My name is Dr. Brian Dressen, a chemist who specializes in developing protections for the warfighter and first response. I have an extensive career background in thoroughly researching and assessing the degree of safety and efficacy of new technologies. My work saves lives. I have no conflicts of interest.

I agree with doctors Rose, Guetzkow, and Setnik in their assessment of the data from the clinical trials. The Pfizer vaccine failed any reasonable risk-benefit calculus in connection with children.

Your decision is being rushed based on incomplete data from underpowered trials insufficient to predict rates of severe and long-lasting adverse reactions. I urge the Committee to reject the EUA modification and direct Pfizer to perform trials that will decisively demonstrate that the benefits outweigh the risk for children.

I understand first-hand the impact that you

will or will not have with the decision you are going to make today. My wife was severely injured by a single dose of COVID vaccine in a clinical trial here in the United States last November. Because study protocol requires two doses, she was dropped from the trial and her access to the study app deleted. Her reaction is not described in the recently released clinical trials report.

Two hundred and sixty-six participants in that trial are described as having an adverse event leading to discontinuation, with 56 neurological reactions being tallied. Since then, we have met trial participants from the other vaccination trials, including the Pfizer 12 to 15 age group trial, who have suffered similar reactions and fate.

Injured support groups are growing. Memberships numbering into at least the tens of thousands. We must do better. Those injured in a trial are a critical piece of vaccine safety data. They are being tossed aside and forgotten.

The FDA has known firsthand about her case and

thousands of others. The FDA has also stated that their own systems are not identifying this issue and that theirs is not designed to identify any multi-symptom signals. This system is broken. My family's life is changed forever. The clinical trials are not appropriately evaluating the data.

The FDA, CDC, and the drug companies continue to deflect the persistent and repeated cries for help and acknowledgment, leaving the injured as collateral damage. Until we appropriately care for those already injured, acknowledge the full scope of injuries that are happening to adults, please do not give this to kids. You have a very clear responsibility to appropriately assess the risks and benefits to these vaccines. It is obvious that isn't happening. I do not wish this nightmare on my worst enemy, let alone a child.

The suffering of thousands continues to repeatedly fall on deaf ears at the FDA. Each of you hold a significant responsibility today. And know that without a doubt, when you approve this for 5- to 11-

year-olds you are signing innocent kids and uninformed parents, who have faith that will undoubtedly rob some of them of their life. With COVID, you get recognition and help, with a vaccine injury you are completely on your own. Thank you for your time.

DR. PRABHAKARA ATREYA: The next speaker is Ms. Linda Mendonca.

MS. LINDA MENDONCA: Think you. I'm Linda Mendonca, president of the National Association of School Nurse, and I have no financial interests or conflicts.

NASN is a nonprofit nursing organization with a mission to optimize student health and learning by advancing the practice of school nursing. In this third school year affected by COVID-19 and following the FDA's full approval of one COVID-19 vaccine, NASN strongly urges all educators, school staff, and eligible students be fully vaccinated. Vaccination is the leading public health strategy to end the COVID-19 pandemic.

Today, this Committee considers extending

emergency use authorization of a vaccine for the prevention of COVID-19 in children 5 to 11 years old. NASN supports vaccination that provides an opportunity to put an end to this pandemic that has resulted in death, long-term ill health, economic hardship, loss of educational progress, mental health challenges, and more.

A recent survey revealed that parents have a strong desire to protect their school-aged children from COVID-19 and the need for increased efforts for continued education about the benefits of vaccination.

As trusted health providers working directly in communities where families live, learn, play, work, and worship, school nurses provide culturally relevant, factual education about the importance of vaccine uptake. It is the position of the National Association of School Nurses that immunizations inclusive of COVID-19 vaccination are essential to primary prevention of disease from infancy through adulthood. Thank you.

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

MR. KERMIT KUBITZ: I am Kermit Kubitz. I have reviewed the FDA analysis of the Pfizer vaccine for persons 5 to 11. I was a polio pioneer in 1955 and am making these comments in memory of my friend, Tom Schifelbein (phonetic), who had polio before that vaccine and later died much too young as a result of the after-effects of that disease.

The FDA analysis presents an adequate analysis of the benefits and risks of lower dose 10-microgram vaccination of young children with 90.7 efficacy. As the FDA presentation notes, there have been more than 44 million COVID-19 cases, with 8.7 occurring among 5- to 11-year-olds with 146 deaths. Hospitalized children with chronic lung disease, obesity, and neurologic disorders were at higher risk. The benefit-risk ratios and comparative scenario analysis presented in Table 14, shown as my primary figure of merit, prevented COVID-19 ICU admissions versus excess myocarditis ICU admissions.

For the scenarios which I view as most realistic, Scenario 2 with the Delta peak of August

2021, and Scenario 4, the 90 percent efficacy against September 11th occurrence, approximately a four to three ratio of ICU admissions, 77 to 80 per Scenarios 2 and 4 for vaccinated children versus 58 for the placebo group. This positive benefit ratio supports vaccination for 5- to 11-year-olds.

And other policy considerations also do, including suppressing virus reproduction and variant development, protecting the rest of the population including immunosuppressed or unvaccinated individuals, and reducing possible long-term effects, i.e., long-term COVID, such as my friend Tom Schifelbein had from polio.

I would have preferred a benefit-risk tabular summary in the form used by the FDA for structured benefit-risk with five questions and answers. One, what is the medical condition? Two, what are the available alternative treatments? Three, what are the benefits of the treatment? Four, what are the risks of the treatments? What is the summary benefit-risk? Moreover, a structured benefit-risk table would have

been more informative and convincing to medical professionals and families facing the decision to vaccinate.

However, given the analysis presented, vaccination of 5- to 11-year-olds is still supported. Thank you.

DR. PRABHAKARA ATREYA: Thank you. The next speaker is Ms. Kristi Dobbs.

MS. KRISTI DOBBS: Yes, hi. I want to acknowledge to the Committee that I attest I have no financial conflict of interest. And also, in my speech, I want to note that I have permission to discuss a minor patient from her mother.

My name is Kristi Dobbs. I'm a dental hygienist, wife, and mother of four. I am pro-science and I believe in good medicine.

I received my first and only dose of the Pfizer COVID-19 vaccine on January 18, 2021. I had an immediate reaction at the hospital clinic where I was appointed. My initial reaction was a tingling sensation in my left arm where I had just received the

shot. I felt as though water was dripping inside my arm. I had barely sat down in the monitoring station when I suddenly had a pre-syncopal episode. I couldn't breathe, felt hot, I had increased pulse, respirations, and heart rate, as well as a blood pressure reading that was so high it was stroke worthy.

The next two days following my Pfizer vaccine, my symptoms included sore arm, fatigue, swollen lymph nodes, and a headache. These are all the normal side effects I anticipated and was given as informed consent.

However, on Day 3 after the inoculation, the effects of the vaccine started to ravage my body. I had sharp, stabbing pain in my left scapular region, as well as paresthesias and tremors in my left arm and hand. By day four I was having full body tremors and paresthesias, as well as an internal electrical vibration feeling, tinnitus, extreme fatigue, brain fog, muscle pain and weakness, inability to sleep, and multiple autonomic dysfunctions.

I have had over 22 different symptoms that

have plagued me over the last nine months. To date, I have seen over 15 different medical providers and specialists. Back in March, I even had a telehealth visit with one of Dr. Naik's colleagues, Dr. Safavi, at the NIH. And I have been specifically told not to vaccinate my children. I have sent my blood to the NIH as well as prestigious universities and private researchers looking for answers.

My vaccine injury has been reported to Pfizer, Bayer, CDC, FDA, NIH, and other prominent research facilities. Messages and meetings have transpired between the vaccine injured and top officials at the CDC and FDA including Rochelle Walensky, Peter Marks, Janet Woodcock, and Paul Richards. They have all known about these COVID-19 vaccine injuries since at least early this year.

I have met countless others that have been injured by the COVID-19 vaccines. And, because of the intentional suppression of these reactions, the injured have been unable to get essential medical care, research for treatment, and there is clearly no

recovery plan or financial support.

We are being silenced, abandoned, and cast aside as collateral damage. I have met 13-year-old Maddie de Garay who is severely injured and is now confined to a wheelchair with a feeding tube after receiving her Pfizer COVID-19 vaccine under clinical trial. She has been given no real medical help, abandoned by Pfizer, the test clinic, and the FDA. Her adverse event was coded as nothing more than a stomachache, and her mother fights every day for answers and help while watching her child endure this painful journey.

I accepted my vaccine as a personal responsibility to my family, community, and country. She chose to participate in the vaccine trial as a brave 12-year-old child wanting to beat COVID and get back to normal. We were wrongfully coerced into taking this vaccine by prominent politicians, world health leaders, and renowned medical directors of this country. We were told that these vaccines are safe and effective, but Maddie and I are living proof that these

vaccines are not safe nor effective.

If we impose these vaccines on our most vulnerable, our children, it will be an absolute crime against humanity. If this happened to us, it will happen to more. We have got to protect our children. They are our future. We are real, not rare.

DR. PRABHAKARA ATREYA: Thank you. The next speaker is Dr. Dorit Reiss.

DR. DORIT REISS: Hello. Thank you for the opportunity to comment. My name is Dorit Reiss, and I am a professor of law at the University of California, Hasting College of the Law. And I have no conflict of interest.

I appreciate your careful analysis of the data on this, and I want to add three points for your consideration on top of everything you've already heard. First, I want to remind you that the risk and benefits of vaccines need to be considered in context. In this case, I want to remind you that in 12 states, there are prohibitions on requiring masks in school either through the law or through executive order.

This includes large states such as Texas with 28 million or Florida with 20 million and many others. In those states, there are battles around masks, but the reality is that many parents just don't have the option to send their children to school without taking any precautions to reduce COVID-19. And, in several states, they no longer have an online option. And this is often on the background of high community transmission rates and hospitals filling with children. As we're seeing, and as was set out, cases in children and hospitalizations of children have increased.

Authorizing vaccines for 5 to 11 would give these parents the choice of vaccinating the children and allow them to offer some protection, both for the child and in families that have an immune-compromised member to the immune-compromised member. Since children bring back COVID-19 from school is a very realistic option for some families. And it's the hardest for families that don't have the resources to pull their children out. Please give parents the option to protect their children.

My next two points are as an administrative law professor. I have studied advisory committees. First, I want to remind you that as an expert advisory committee, which is concerned to advise the FDA about the data, your job is to provide an objective, knowledgeable review of the information drawing on your expertise. That means that when misinformation or disinformation, such as the misuse of various reports is raised before you, your job is to ignore it and focus on the actual data. And you should also treat unverified anecdotes with some caution because you really need to focus on the data.

I expect you'll do it anyway, but thought it worth reminding you that, when you are ignoring this information and when you're cautious about unverified stories, you are doing the right thing. Your decision should be based on actual facts.

Finally, I want to say something about mass commenting complaints. Yes, a lot of comments have been submitted to the written comments. I want to remind you that, although mass commenting complaints

are not usual for expert advising committees and they are probably inappropriate for this Committee, they are not unusual in rulemaking for some agencies.

And the way agencies usually treat them in rulemaking is as if they were one big comment raising the issues, if we're talking about form comments that repeat the issue. Substantive and quality is what matters, not the number of comments per se. It's not a vote. Mass commenting complaints are not generally representative, and the agency knows it. And agencies are required to follow data, not votes. This is even stronger for advisory committees. Advisory committees are not a representative body; they're not there to reflect community opinions, but to provide expert input.

Even if the mass comments were representative, and they're not, your job would be to provide analytical input based on the data. We have other ways to measure political will, and that's the job of the political executive, not the Advisory Committee. Thank you.

DR. PRABHAKARA ATREYA: Thank you, Dr. Reiss. The last speaker for the session is Ms. Brooklyn Aaron.

MS. BROOKLYN AARON: Hi, can everyone hear me?

MR. MICHAEL KAWCZYNSKI: Yes, we can. Go ahead.

DR. PRABHAKARA ATREYA: Yes.

MS. BROOKLYN AARON: All right. My name is Brooklyn. I am an ethics fellow at a health system but I'm not speaking on the institution's behalf, and I have no disclosures.

There's a reason we're focusing on a benefit-risk analysis today. An ethical vaccine is one that is anticipated, to the best of our knowledge, to result in risks that are proportionate to the benefits provided with the benefits outweighing the risk. I wanted to draw a parallel to a widely accepted medical decision-making model for minors, the best interest standard.

The right decision is the decision that best promotes the interest of the child. This is how, if approved for EUA, I am making the decision whether to vaccinate my preschooler. COVID-19 vaccination for her

may not be justified on the sole basis of physiological benefits given the low severity rates in her age group. However, a study completed by the Leukemia and Lymphoma Society demonstrated that one in four blood cancer patients failed to produce detectible antibodies after two doses of either Pfizer or Moderna.

Patients with these malignancies were least likely to produce detectible antibodies, and common treatments for those diagnoses target B cells indiscriminately, resulting in the inability to produce antibody responses to either vaccines or illness.

I am one of those patients, so I've had to weigh for my child the extreme risk of losing a parent, against the risk of not letting her leave the house. Although we don't have full data on transmission, we do know that transmission is less likely if more people around an individual are vaccinated.

A vaccine is not going to be a hundred percent effective at its aimed to prevent serious diseases. It's not going to be 100 percent safe. But we have taken steps to reduce already rare risk of the vaccine

such as reducing the dose of the vaccine.

The extreme isolation and stress and emotional deterioration the world experienced for just a few weeks of shutdown, there are children still experiencing that. This vaccine adds another layer of protection for us. For my preschooler, the risks of being vaccinated don't come close to the risk of continued isolation to the level she must adhere to now.

For her, everything hinges on this vaccine. It might not be worth the potential risk for every child, and I accept that. But the data as presented, the vaccine accomplished the aim unprecedentedly well. To the best of our knowledge, it's safe. You should now allow parents to weigh the benefits and risks for their children and at least give us the option.

MR. MICHAEL KAWCZYNSKI: All right. Thank you. Prahba?

DR. PRABHAKARA ATREYA: Thank you. We thank all the OPH speakers who expressed their viewpoints today. This concludes the open public sharing session.

And I will turn the meeting over to Dr. Monto, our chair today. Thank you.

DR. ARNOLD MONTO: And I think we now have a break which go on until 2:10 Eastern Time. So about seven minutes until we reconvene.

MR. MICHAEL KAWCZYNSKI: All right. Thank you, Dr. Monto.

[BREAK]

ADDITIONAL Q & A REGARDING SPONSOR AND FDA PRESENTATIONS

MR. MICHAEL KAWCZYNSKI: Okay. Good afternoon and welcome back to the 170th VRBPAC meeting. We are now going to get into our -- this is our final session run for the day. We are now going to go back to -- start with our Q&A in the afternoon. So, Dr. Monto, are you there?

DR. ARNOLD MONTO: I am.

MR. MICHAEL KAWCZYNSKI: All right.

DR. ARNOLD MONTO: Since we ended abruptly with Dr. Yang's presentation on the various risk-benefit scenarios, I thought we'd start out by having her and her colleague, Dr. Forshee, answer any questions that the Committee has, and then move to a more broad question and answer session involving both FDA and the sponsors. So I see Dr. Offit has his hand raised. Dr. Offit?

DR. PAUL OFFIT: Yes. First of all, thank you, Dr. Yang, for a very thorough presentation. Let me ask this question. Were you to include the data that were presented by Dr. Havers, where she found that 40 percent roughly of 5- to 11-year-olds were seropositive? Your analysis, and correct me if I'm wrong, assume that all 5- to 11-year-olds were susceptible to illness. She showed that many likely weren't, or at least arguably were not susceptible to serious illness.

So, a parent could reasonably say, my child is seropositive. I think they're likely protected against serious illness. There's much still not known about

myocarditis. I'm going to choose to wait. I mean, so how would you -- first of all, how do you think it would change your analysis, and what would you say to that parent?

DR. HONG YANG: Yeah. Right. (Inaudible) assumption, we do have a data balance. CDC consider that that's imperative (inaudible) support these groups. There's no vaccine for this group. So, basically, we account for everyone in this group, consider them susceptible to this disease.

Based it's on what you say, if it's 45 percent of individuals in this group or they have immunity, and then the cases that will be -- I don't know what about the potential of those immunities because it depends on -- we are not clear if someone tests positive how will be the protection. So, if you assume those individuals has immunity test positive in antibodies, they have the same kind of the protection as the vaccine.

Then basically, you have 45 percent reduction of the other benefit. We don't have that data. We don't know if someone tests positive what would be

their antibody titer. How is the protection compared to that vaccine? Because there is also some literature based on -- for the adult population. Actually, if someone got infected, they still are vulnerable to the COVID infection. So we don't have the data for the (inaudible).

DR. PAUL OFFIT: You're usually not as -- if you can develop an antibody response, it's likely you've developed a memory response, although you're right. I think that you may not be protected against asymptomatic or mildly symptomatic infection. You are probably, likely protected against serious illness after an actual infection, which would change your sort of hospitalization rates, but you're right. I mean, what one does, that's another piece of information that's lacking, but thank you very much for that answer.

DR. ARNOLD MONTO: Thank you, Dr. Offit. Dr. Sawyer?

DR. MARK SAWYER: I'd like to call up Dr. Offit's question and go back to a question Dr. Kurilla

asked at the very beginning that influences this same issue of estimating hospitalizations prevented and ICU stays prevented. That is the question of children who are hospitalized for some other condition but just happened to have a COVID test done as a part of the routine testing of all admissions to the hospital.

I believe Dr. Havers estimated that only 20 percent of the patients in the COVID net data fit that category. I'm wondering if you could address how you dealt with this issue in making your estimates.

DR. HONG YANG: So --

DR. RICHARD FORSHEE: So, Hong, I'll take a stab at that. I actually hoped that someone from CDC might be able to comment a little bit more about how they actually coded those cases because we don't have the details. We were relying on the COVID-NET data. So, I'm curious if anyone from the CDC can comment on that.

DR. ARNOLD MONTO: Do we have anybody --

DR. RICHARD FORSHEE: Dr. Havers, I believe you're on mute.

DR. ARNOLD MONTO: -- from the CDC in the group? Another question I'd like to ask CDC is how representative they believe the antibody prevalence is in terms of past infections because from some of the cohorts we work with, the antibody prevalence is far lower, depending where you are and what the precautions have been. So, Dr. Havers?

DR. FIONA HAVERS: Yeah. No. I'm happy to take both of those questions. To answer the first question regarding, how we determine the proportion of patients that are actually determined? When they are admitted with a positive SARS-CoV-2 test, if it's primarily related to COVID-19 related illness, or incidental on screening.

Again, in COVID-NET data, we have detailed information on all of the pediatric admissions and someone has -- a trained surveillance officer has reviewed the medical chart, and, based on the reason for admission, the chief complaints, and other information, they determined whether or not it's COVID-19 related illness. If there's any question about it,

they add in (inaudible) information, and then we have two physicians that review the reason for admission and other information.

We did find that for older children, for adolescents, that the admission rate for probably nine COVID-related reasons was higher. In adolescents, we found that the proportion was higher than 20 percent because there was a fair proportion of adolescents who were admitted for, like, if they were pregnant and were admitted for labor and delivery, caught on screening or for mental health like suicide attempts or overdoses.

But any 5- to 11-year age group, we saw it was about 18 or 19 percent that we think was most likely related to something -- the primary information was not a COVID-19 illness. Many of the children may have been -- were symptomatic, even if they were categorized as that if they were admitted for an elective surgery or trauma or something else that was sort of more clearly not COVID related. But it is sometimes difficult to tell.

So, I would say that the rates are a little

bit higher. I mean, the rates include all of the positive SARS-CoV-2 tests with children with positive SARS-CoV-2 tests. But there is a proportion of children that may not have been admitted for COVID-related illness primarily.

Again, among the children that are admitted and whose primary reason for admission is COVID-19, we do see a fairly large proportion of patients that have severe outcomes, at least a third of those are admitted to the ICU. In relation to -- did I answer your first question there?

DR. MARK SAWYER: Yes. Thank you.

DR. FIONA HAVERS: Okay. And then Dr. Monto, you had a question about the seroprevalence studies that we're looking at the antibodies in children.

DR. ARNOLD MONTO: Right. It was at 40 percent because I can tell you, from some of our own populations that you know very well, it's far lower than that.

DR. FIONA HAVERS: Yeah. No. I think that those are good questions. I think the different

methodologies do yield different results. I think, as I mentioned before, these were from national seroprevalence studies that were -- we used select -- the investigators for this study did select jurisdictions where they had a decent number of pediatric specimens, that they are from residual clinical specimens. So, it's children presenting for clinical care.

Again, they may not be totally representative of the general population. Most of them are probably in this age group receiving cholesterol screenings, which is recommended for children in this age group. So, we don't know that that's that big of a limitation. One, the other thing I would say is that seroprevalence estimates vary a lot depending on the assay that is used.

This is one that that, one, that they limited this seroprevalence study too is one that has a pretty high sensitivity and generally doesn't wane over time. So, that may have given it higher estimates than you would see in some other seroprevalence studies that use

different assays.

Again, I think there are other data out there, and I would reemphasize that even when the results from the study show that there was a 40 percent seroprevalence in this particular population. That was over the summer. Even since then, we saw the highest hospitalization rates in the 5- to 11-year age group in September during the Delta wave. So, there's clearly a lot of susceptible children still out there that are vulnerable to severe disease. So, I just wanted to make that point as well. So, thank you.

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

MR. MICHAEL KAWCZYNSKI: Dr. Meissner, you don't have to wait for your camera to come up to start speaking. Go ahead.

DR. CODY MEISSNER: All right. Thank you, Dr. Monto. I have a question also for Dr. Yang. First of all, I appreciate the model that you presented and the sensitivity analysis that you included and -- because, as we all know, it's the base case assumptions that are made that determine the reliability of these sorts of

the model.

But the point that I wanted to make is that, I believe you said you took data from the week ending September 11, and I just want to point out that that was the peak of the fourth or the fifth wave of this pandemic. At that time, the rates of hospitalization were in the 5- to 11-year-old group coming from the CDC data was 1 per 100,000. Over the last few weeks, that number has fallen to 0.4 per 100,000.

There's some suggestion that this pandemic may be evolving into a pandemic as more and more people acquire immunity from the vaccine and from infections has been noted. So, in a way, you've taken the worst-case scenario, and it is not really reflective of what we're seeing at the present time. Obviously, it's very hard to predict what's going to happen with this virus. No one can say for sure.

I think it is important to look at your analysis. I think you looked at a 10 or 20 percent lower rate of disease, and that was just low. The factors are it seems to be less than 50 percent

counting the numbers during the period that you took your base case. Thank you.

DR. ARNOLD MONTO: Response, please.

DR. HONG YANG: Yeah. So, our scenario, we have Scenario 2 and 3. The reason we have that two scenario is because we think that a future pandemic is unsettling. So, the Scenario 2 is the peak. We take a peak. So, actually, you are right. Our base of Scenario, September 11, is close to the recent peak, but we do have Scenario 3. We take the lowest point. So, the lowest point, the incidence rate for the cases is five percent for the September 11.

The incidence for hospitalization is a ten percent of our base rate on September 11. So, basically, we use these two scenarios, Scenario 2 and 3, as upper bar and lower bar. Of course, we still cannot totally rule out the incidence can go beyond these two bars, but we think it's less likely. So, that is the way we try to see how the impact of the future pandemic were of the benefit-risk of the vaccine.

DR. CODY MEISSNER: Yes. I think that's a very reasonable approach, and I certainly respect that opinion. But I will just point out that the hospitalizations are now 50 percent lower than they were during that time period.

DR. HONG YANG: Right. So, the low --

DR. ARNOLD MONTO: Thank you, Dr. Meissner. I'd like to go on to Dr. Fuller.

DR. OVETA FULLER: Thank you, Dr. Monto. This was actually very informative with the modeling and the FDA comments. I have a couple questions, but I'll first ask the one of Dr. Yang. We know that parents are wanting -- most parents want to do what's best for their child and is going to make a decision should these vaccines become available based on their particular situation. So, I found that your scenarios were very, very helpful.

We don't know what's going to happen. We're in an unprecedented pandemic. We don't know if the virus is going to go up or if the -- we just don't know. So your scenarios were very helpful. My

question is, with other vaccines, such as HPV or chicken pox or others that have been approved, have we ever had the value of this sort of scenario predictions before?

Then the other question is perhaps for Dr. Wong about the BEST system, in terms of following long term what happens. How long have we been doing that to the degree that we can be able to pick up something that is happening at a lower frequency, but at a longer term? There's no precedence of this, but I really am comforted by the fact that these are in place.

And my question is, have you done this modeling with any other vaccines in terms of -- I know we're not in a -- have not been in a global pandemic with them, but has this sort of modeling scenario been done before?

DR. HONG YANG: So, to answer your question, FDA will really (inaudible). We always conduct the benefit/risk assessment. For that kind of the formal analysis is -- now, we don't do this for every (inaudible) because it does take a lot of effort. So,

we usually only do this when there is a very challenging issue, also of the important that is difficult to speak to the (inaudible). Then we have four more analyses.

DR. OVETA FULLER: I found it very (inaudible) --

DR. HONG YANG: (Inaudible) --

DR. OVETA FULLER: -- so I wanted to thank your team for doing this. Then my question, if I might, Dr. Monto, to Dr. Wong, or do you want me to hold it till later?

DR. ARNOLD MONTO: Let's come back to that.

DR. OVETA FULLER: Okay.

DR. ARNOLD MONTO: Because I just want to get this clarified, and then we still have plenty of time for a broadened discussion. Dr. Lee?

DR. JEANNETTE LEE: Yeah. So, thank you for that presentation, Dr. Yang. I think one of the questions I have, I think, what troubles some people was the scenario 3, and the fact that what we've seen was a pandemic as sort of a wave that sort of peaks,

and then there are valleys and so forth. The question is, is there a point at which this would not really be advised? I don't know that we can predict that.

I guess the other question I have related to this, and I'm really very pleased to see this modeling, is to what extent is there the potential for actually sort of fine-tuning this, not necessarily in this scenario, but in terms of stratification by age and other demographic characteristics, as well as the fact that I think we recognize that the incidence rates, the vaccine efficacy, the death rates, and all of those vary quite a bit regionally, and whether or not those things can be used to sort of help make decisions. Thank you.

DR. HONG YANG: Yeah. So that is a good question. So, we understand a lot of benefit-risk probably is not uniform. So, it depend on a lot of comorbidity and also demographic characteristics. But to test for modeling, we do need information. So a lot of this kind of information, for example, efficacy. We don't have the efficacy for (inaudible) in small

populations, and they may too have different characteristics.

Also, a lot of (inaudible) for the model enclosed, we were also (inaudible) that if we want to do the (inaudible) analysis, we will need to have each set by those subgroups. You will need to have efficacy by those subgroups. So, that is really -- we have a (inaudible) limitation on the data for that kind of the more structural analysis.

DR. JEANNETTE LEE: Great. Thank you.

DR. HONG YANG: So I think that is a good suggestion. Yeah.

DR. ARNOLD MONTO: Thank you. Dr. Cohn?

CAPT. AMANDA COHN: Thank you. Dr. Yang, I just wanted to ask about your assessment of the myocarditis cases, and I know that you mentioned several times that it was the highest possible -- the highest anticipated rate of myocarditis that you're making in this age, but, based on the presentation from earlier this morning, it seems like the likelihood of this age group having even close to those same rates of

excess cases of myocarditis given they're receiving both a third of the dose and they have such lower rates of myocarditis in this age group, anyway.

It seems like the -- I believe it was the fourth or fifth scenario where you used even the Bayer's number of reports for the 12- to 15-year-olds is a closer estimate of the number of cases of myocarditis you would expect. So, I was wondering what your thoughts were on that and how you determined which data to use to support your rates of myocarditis.

DR. HONG YANG: So, to test for myocarditis, we do look at different database, like the data from vaccine safety data link, also VAERS, the Vaccine Adverse Event Reporting System. For all those data, we also have our own FDA symptom of BEST system.

So, for all those, they have limitations. But for this purpose, we feel like the BEST system uses the half-pan data (inaudible) because for VAERS system, there's no denominator.

So, the reporting is a voluntary reporting. That is not as we want (inaudible). Also, we don't

know what is the percentage. It's difficult. The weight derived from the VAERS data, we still -- it's likely under-reporting because --

DR. AMANDA COHN: But what about in comparison to all the other countries that have reported rates of myocarditis in younger adults or adolescents? Aren't those also mostly lower than what the BEST data is reporting?

DR. HONG YANG: Yeah. We do also look at the other countries' data. So one thing is different country have different populations. So that data sometimes is not really representative. Also, we are not very familiar and confident with the other countries' recording system. We don't know what is their limitations, how to really interpret the data, how that will apply to our system. So, we feel like a few -- yeah, maybe Dr. Rich Forshee may relate it more about that.

DR. RICHARD FORSHEE: Yes. Dr. Cohn, I just want to say that your basic point is correct. The estimates that we're using are likely to be significant

overestimates, so what the myocarditis rate is likely to be in the age groups that we're looking at. There simply isn't any population levels data on this age range since it hasn't been used in this age range yet. So, there were very limited options for what we were going to use to ground our analysis.

That's why we've tried to emphasize all of the reasons that we do think it's likely to be the maximum possible estimate and why we estimated scenarios to reflect the possibility that we could have a 50 percent lower myocarditis rate in this age group. We can revisit this as more data are accumulated, but we chose to use the closest age range for which we had national level data to inform those rates and do sensitivity analysis to assess the possibility of the likelihood that the 5 to 11 age range would have a lower rate. That was the approach that we chose.

DR. ARNOLD MONTO: Thank you. Dr. Portnoy, and, after this question, I'm going to try to open this up. We'll continue with the people who had their hands raised, but I'm going it up to more general questions.

You've been grilled for long enough. Dr. Portnoy?

DR. JAY PORTNOY: Thank you. Gosh, I'm a little disoriented because the video is lagging behind the audio. Can you hear me okay?

DR. ARNOLD MONTO: We can hear you. Go ahead.

DR. JAY PORTNOY: Okay. So I guess my question -- I want to go back to the concept of children already having been infected with the COVID and having some immunity already. Do we know how good that immunity is, how protective it is, and how quickly the children who have had COVID before get reinfected?

We're giving vaccines to patients who are likely to have been infected in the past. We're not going to probably insist that serology be done before we get these vaccines. So a lot of the people who get the vaccine are likely to have already been infected. Do we know how previous infection changed the response to the vaccine, and in particular, how it changes the likelihood of having adverse effects from the vaccine? Do we have any information about that?

DR. RICHARD FORSHEE: So, Dr. Portnoy, I know

that we have some data on the effectiveness of the vaccine when it's given to people who have previously had a case of COVID-19, and the CDC has published in MMWR showing that there is significantly reduced likelihood of hospitalization when the vaccine is given to people who have previously had the COVID-19 infection.

I'm not familiar with studies looking at differences and the adverse event rates. Given that myocarditis is a rare outcome, it may be difficult, certainly using claim space systems. That would be very difficult to reliably identify people who had COVID-19 previously to see whether that was an effect modifier for the adverse events. So that's what I can add there. Maybe others who could add more as the conversation goes on.

DR. ARNOLD MONTO: Thank you. Dr. Kurilla?

DR. MICHAEL KURILLA: Thank you, Arnold. Let me just make one comment reflecting Dr. Portnoy and actually getting back to Dr. Offit's comment about the risk of reinfection and whether or not prior infection,

the degree of immunity. Pfizer does have in their briefing package, they make a comment that in the subset for immunobridging, that they saw no cases of infection in any of that subset that had demonstrated prior infection. So one could, if it's a small number, say the prior infection was 100 percent efficacious. At the very least, it's probably as good as vaccination. So, that's just one little data point.

For Dr. Yang, you may have said this, and I missed it, but your scenarios were done over what time frame?

DR. HONG YANG: Six months, post second dose.

DR. MICHAEL KURILLA: Six months, okay. So, did you assume that the efficacy of the vaccination that they demonstrated at two months was going to be in effect for the entire six-month period, or did you actually use the Pfizer data on adults, which shows waning immunity over that six-month time frame at least for infection?

DR. HONG YANG: No. So, in our model, we did not model the dynamic of the vaccine efficacy changes.

So, our one assumption is we keep the constant of efficacy over the six months.

DR. MICHAEL KURILLA: So you assume that the 90 percent efficacy is going to hold up for six months?

DR. HONG YANG: No.

DR. RICHARD FORSHEE: Excuse me --

DR. HONG YANG: Our --

DR. RICHARD FORSHEE: -- Dr. Kurilla, that was only one scenario that we used that. I'm sorry, Hong. Please go ahead. I think you'll talk about the base scenario.

DR. HONG YANG: Yeah. So the basis -- so, basically, we did not use 90 percent. Ninety percent is the higher efficacy based on the new supplemental analysis submitted by the sponsor. Our base scenario actually used 70 percent efficacy. So that data is based on CDC's study of the vaccine. That (inaudible) study, and they look at the period for (inaudible) period of the Pfizer vaccine. So, we based scenario -- we used 70 percent again the cases, 80 percent again to the hospitalizations.

DR. MICHAEL KURILLA: Well, no, but I'm specifically talking about the cases, which by six months, the Pfizer vaccine in adults at least is waning significantly in terms of preventing infections and you made no assumptions about asymptomatic infections in this population at all either, correct?

DR. HONG YANG: No. So ours only look at the systematic cases. Our assumption is 70 percent of again the cases. We assume the efficacy, 70 percent, is confident over six months.

DR. MICHAEL KURILLA: Okay. Thank you.

DR. ARNOLD MONTO: Okay. We're going to have to move on. We've got a --

DR. RICHARD FORSHEE: Dr. Monto, could I make one final point?

DR. ARNOLD MONTO: -- we're only (inaudible) discussions -- I mean, our question time. Dr. Hildreth, I think you've had your hand raised for a while. Again, you can ask questions of anybody at this point.

DR. JAMES HILDRETH: Thank you, Dr. Monto. My

question's related to something others have raised, which is whether or not Scenario Number 3, which I asked earlier, is the one that's most relevant to our current situation. And, if the trends continue the way they are going, the emergency for children is not what we might think it would be, and that's just my main concern is whether or not the scenario you used to model this is the appropriate one for where we find ourselves at right now? So that was it, Dr. Monto. Thank you.

DR. ARNOLD MONTO: Okay. Would you like to answer, or is that something --

DR. RICHARD FORSHEE: I can make a brief response to that. This has been discussed a bit so far that it is unpredictable, what the path of the COVID-19 pandemic is going to be from this point going forward. We do recognize that the model is sensitive to the incidence rate for COVID-19. So that is one of the most important factors on what the benefit-risk balance is going to look like.

I do want to say that when we built these

models, we were trying to make conservative assumptions throughout. I think the one thing that's come up in this discussion that we didn't add is an additional conservative assumption is a natural immunity from prior COVID infections. But we think that we're using a very high rate for the risks of myocarditis, pericarditis, and we are looking primarily at the hospitalizations and ICUs for COVID-19.

This morning, there was discussion of many other implications of the COVID-19, that there can be other long-term effects that people in this age group experience that were not included in the model. So, overall, we think we used conservative assumptions, but it is sensitive to the COVID-19 incidence rate. Thank you.

DR. ARNOLD MONTO: Thank you. Just as a parenthetic comment, we've been assuming that we're on the descending slope of the curve previously and been caught flat-footed as the rates again went up. So, I'm thinking that this is going to be the end of the wave permanently is maybe a little overly optimistic. Dr.

Perlman.

MR. MICHAEL KAWCZYNSKI: You're muted, Dr. Perlman. Actually, Dr. Perlman, let's make sure you reconnect your audio, and we're going to go to somebody else at this time.

DR. ARNOLD MONTO: Okay. Dr. Rubin?

DR. ERIC RUBIN: Thank you. I actually went to put my hand up for following discussion when you said that (inaudible).

DR. ARNOLD MONTO: Well, we are in open. I'd like to get off -- that's just the point. Let's open up the question and answer.

DR. ERIC RUBIN: Well, if I could, and this may be a question for Dr. Havers, who may be in the best position to answer it if she's still around. In the discussion --

DR. ARNOLD MONTO: Yeah. She was. But let's hope.

DR. ERIC RUBIN: We have been talking about the risk-benefit analysis, which is incredibly helpful, by the way, for the vaccine. Obviously, there are some

close calls here using a population (audio skip).

DR. ARNOLD MONTO: I think you're breaking up.

MR. MICHAEL KAWCZYNSKI: Here, Dr. Rubin, I unmuted you because you keep getting a -- there you go. Go ahead.

DR. ERIC RUBIN: Okay. Yeah. I got muted without touching anything.

MR. MICHAEL KAWCZYNSKI: Yeah. That's all right. Take it away.

DR. ERIC RUBIN: Sorry. So, I don't know where you lost me. I guess the question is, can we identify a particularly at-risk population that we should have a vaccine for right now among 5- to 11-year-olds where it would be important to improve it apart from a population level effect?

DR. ARNOLD MONTO: Dr. Havers, that's to you.

DR. FIONA HAVERS: Thanks for asking that question. And may I say --

DR. ARNOLD MONTO: That's a tough call.

DR. FIONA HAVERS: That is a tough call. I mean, I do think that we have identified that children

with underlying medical conditions are at higher risk for hospitalizations and severe outcomes. Although many of the underlying medical conditions that put children at higher risk are very common in the population. So I think that that would be very challenging to sort out.

We are seeing higher rates of hospitalization and severe outcomes among children of different ethnic groups, as I said. Although once we adjusted for underlying medical conditions, that they did not appear to be at higher risk for severe outcomes conditional on being hospitalized. So, I think it would be very difficult to narrow it down to a specific population, although we do know that children with underlying medical conditions are at higher risk.

I will point out, though, that a third of the children that are hospitalized do not have an underlying medical condition that is identified prior to hospitalization. And so there --

DR. ARNOLD MONTO: What proportion --

DR. FIONA HAVERS: -- are a lot of healthy

children. Pardon?

DR. ARNOLD MONTO: What proportion of those hospitalized are previously healthy children? Can you guess?

DR. FIONA HAVERS: Yeah. About 30 -- well, a little bit over 30 percent of the children that are hospitalized don't have any underlying medical conditions in this age group.

DR. ARNOLD MONTO: Okay. Thank you. That's very helpful. Dr. Perlman, can we connect you now?

DR. STANLEY PERLMAN: Can you --

DR. ARNOLD MONTO: We can.

DR. STANLEY PERLMAN: Okay. I just had some questions for the sponsor, if I could.

DR. ARNOLD MONTO: Please. We've let them get off so far.

MR. MICHAEL KAWCZYNSKI: All done.

DR. WILLIAM GRUBER: I'm back. I'm back.

DR. STANLEY PERLMAN: Okay. So, we heard about some of the measurements of antibodies, and what I was curious about is two or three things. One is, do

we have any information about T cell responses in these children? And second, I know there's some samples drawn at the six-month mark. Do we have any information about the duration of the antibody? I think that was answered earlier, but I just wanted to confirm that.

The third question is, something that was actually raised in the public discussion, which I had - and I had the same question. Namely, what do we know about the degradation of the RNA vaccine with time in these younger children? Is it the same kinetics of degradation as we see in older populations? Do we know anything about that?

DR. WILLIAM GRUBER: Thanks, Dr. Perlman. Let me sort of address the first question. I think the first question was about the nature of antibody we have -- are antibody response, one of the first two questions about the length of antibody response. Again, we have six months sera drawn, but we don't yet have those data. Obviously, we'll be interested in that.

As far as T cell responses, as you may recall, we've done significant studies in adults, demonstrated robust TH1, CD4 and CD8 T cell responses. We plan additional analysis with our partner BioNTech in 5- to less-than-12-year-olds. We've got about 30 of them. The testing is being done at BioNTech, but we don't have that data yet.

Then as far as the stability issue is concerned or what happens to the mRNA, I don't know that I can speak to anything in terms of the pediatric population, but we know about animal studies where, again, the safety profile was quite (audio skip).

DR. ARNOLD MONTO: Thank you. Dr. Nelson?

DR. MICHAEL NELSON: Thank you, Dr. Monto. As a practicing allergist/immunologist caring for adults and children with compromised immune systems, and in light of the COVID-NET data this morning showing that 68 percent of the hospitalized patients have at least one comorbidity, I have a couple questions about some of our higher --

DR. STANLEY PERLMAN: Same here.

DR. MICHAEL NELSON: Is there any subset of immunobridging or reactogenicity data for the 20 percent or 312 in the sponsor data set presented this morning? And do the proposed sponsor post the EUA authorization studies include proactive study of immune responses for children with compromised immune systems from underlying disorders or related treatment?

Lessons learned from the rollout in the older age group demonstrated the value of additional doses as early as two months after the primary series. Hopefully, we won't need to wait six to eight months to know that there are some high-risk patients with no response.

DR. ARNOLD MONTO: And those that are given a third of the dose. So, Dr. Gruber, do you have an answer?

DR. WILLIAM GRUBER: Yeah. So let me address the first one. I think the first question was focused on the nature of antibody responses and those with underlying comorbidity and we do have an analysis of that. If we can bring Slide 1 up. This represents a

circumstance where we have individuals grouped together as the entire group as well as those that have an underlying comorbidity listed as yes and those that don't listed as no.

And I think you can appreciate that the nature of the response looks quite comparable whether we're talking about the entire group, those with comorbidities or those without. As I already indicated, we'll obviously be monitoring real-world evidence as well as antibody responses over time to see about the potential for decline and when a boost might be necessary.

DR. MICHAEL NELSON: Right. But any sense as to within that comorbidity subset as those that actually have comprised immune systems or were on immunosuppressed treatment?

DR. WILLIAM GRUBER: No. No. Let me be clear about that. These are individuals who did not have immunosuppressive conditions. We do have additional studies, actually, that have started in terms of children with immunocompromising conditions, and

actually in all the age groups from greater than 2 years of age up to 18. This includes individuals that are receiving immunomodulator treatment for autoimmune disease.

That also includes individuals post solid organ transplantation and those that are post-bone marrow or stem cell translation. So we will have some of that data to inform how best to use the vaccine in those (audio skip).

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

DR. HAYLEY GANS: Thank you very much for this opportunity. I had questions for both the CDC, the FDA, and Pfizer. So I'm just going to try and concentrate on some. So, one of the big questions that I had related to this --

DR. ARNOLD MONTO: Oh, one or two, no more.

DR. HAYLEY GANS: Okay.

DR. ARNOLD MONTO: One or two questions.

DR. HAYLEY GANS: I'll concentrate and come back if we have time.

DR. ARNOLD MONTO: No multiples questions.

Right.

DR. HAYLEY GANS: Okay. So, on Page 12 of the FDA report out in 4.5 post-licensure vaccine doses. It describes 125,000 children within this age group that we're considering today. So below or less than 12 years of age who had received vaccination, I'm assuming it was off-label use. We need to understand if there's any safety data related to the doses that were given. There's a lot of data being followed on vaccine status and that faces hospitalizations, and I think it's very important for us to understand those data. If they're (audio skip).

DR. WILLIAM GRUBER: I think that's a question maybe for the FDA since it's from their briefing doc. I see Doran Fink coming up.

DR. HAYLEY GANS: Yeah.

DR. DORAN FINK: Hi. As far as I'm aware, we don't have safety data for those individuals. Those were numbers that we obtained from CDC. If there are CDC staff who are on the line who might have information about that safety data, they're welcome to

comment.

DR. HAYLEY GANS: And outcomes data, so the CDC (audio skip) for that?

CAPT. AMANDA COHN: Hi. I'll respond on behalf CDC. We do have reports of vaccinees who are less than the age of 12 years. So (audio skip).

DR. ARNOLD MONTO: You're not -- we don't hear you.

DR. HAYLEY GANS: Dr. Cohn, we can't hear you.

DR. ARNOLD MONTO: Mike, is there a problem?

MR. MICHAEL KAWCZYNSKI: Yeah. Dr. Cohn, you're disconnected. Your audio is disconnected at the moment. So she's going to have to reconnect. So we're going to turn her off because we're not hearing her and maybe she'll get the clue.

DR. ARNOLD MONTO: All right. She'll remember the question. I'll call her back, Dr. Gans. Remember, Committee members, we're going to have a general discussion. These could be questions and answers and not discussion. All right. So, Dr. Moore.

DR. PATRICK MOORE: Yeah. I'll just leave my

video off since we're having problems with that. But this is for the sponsor mainly, perhaps for the FDA or anyone else on the Committee here is that what -- this is a new vaccine, and I'm not really certain -- I know why it's being administered intramuscularly, but we're seeing pericarditis or myocarditis as a consequence of this in children.

I'm just wondering is there any effort to look at either animal models or to look at clinical? Is there data from clinical studies that suggest we could give a intradermal injection of this and maybe reduce these side effects? It's really an open question.

DR. ARNOLD MONTO: Well, since it's an open question, let's have a short answer because this is not the question that's in front of us today. So the sponsor --

MR. MICHAEL KAWCZYNSKI: Dr. Cohn is back.

DR. WILLIAM GRUBER: Yeah. So I can give the short answer. We have no data about intradermal administration. Intramuscular administration is common for most vaccines other than those that are given

(audio skip).

DR. ARNOLD MONTO: Okay. Dr. Cohn, let's have your answer.

CAPT. AMANDA COHN: Apologies about that. I have to admit, I was a little embarrassed that I made -- I hung up on us. So we do have doses that have been administered to less than 12-year-olds. I don't know how much you hear me say before, but some of those may have been off-label, but they also may have been misclassified.

So somebody may have put the age wrong, and so we need to go back and look at that data more closely, which we can do. But we don't have any evidence of adverse events being reported in that age group in particular, and as well as no data on outcomes at this time. We'll look at our data a little bit more closely over the next week.

DR. ARNOLD MONTO: Okay. Thank you, Dr. Cohn. I want to remind the Committee that these should be questions for the presenters. We are over time now. I do want to finish all the questions for those that

presented on this complicated topic. So I'm going to go to the end of the list, but we're eating into our general discussion on the voting question. Just be aware. So, Dr. Rubin? Dr. Rubin, are you there?

DR. ERIC RUBIN: Sorry, my mistake. That's an old hand.

DR. ARNOLD MONTO: Old hand, okay. That's a good answer. Dr. Sawyer, is that a new hand?

DR. MARK SAWYER: And this is a question for Pfizer. If I caught the numbers correctly, the original immunobridging population was something over 300 and was whittled down to 264, and I'm assuming there was -- people excluded were excluded because they had pre-existing antibodies showing they had actually been infected. And if so, that gives you a small cohort of 50 or so kids in this age group who we could look at side effects of vaccine after natural infection. And I wonder if you have done that?

DR. WILLIAM GRUBER: Yeah. So, thanks for the question. We actually, by virtue of having to test all of the individuals even with prior evidence of

infection, either derived serologically or based on having a PCR at the time of immunization. There basically was little difference in terms of reaction seen in those that were positive versus those that were negative.

You may remember back to the adult data where, if anything, individuals who had had prior seropositivity might have a little bit of an increase after their first dose, but interestingly enough, they tended to have a lower response in terms of reactions after the second. We saw much the same thing here, but across the board really very little difference.

DR. ARNOLD MONTO: Thank you. We have a few more hands raised, and these are the same questions for the presenters. Short questions. Dr. Meissner, your question.

DR. CODY MEISSNER: Yes. A question for Dr. Gruber, please. As a fellow pediatrician, Bill, I know you understand the concern that people have about the issue of myocarditis of that risk in the 6- to 11-year-old children. And so the question I have for you, did

you, or is it possible, to look for troponin levels or BMP levels in those samples that you've got from participants after the vaccine, thinking about the possibility of subclinical myocarditis?

DR. WILLIAM GRUBER: Thank you. As part of the datasets that we provided to you today, we didn't obtain samples proximate to vaccination when the risk for myocarditis seems to be greatest, right, within the first several days. However, we are taking a very deliberate approach to try to determine whether troponins, first of all, offer any value, in terms of specificity.

So we're taking populations that have already been studied to look at their baseline troponins. We know that you can in some circumstances see false positives. And, while we're doing that, we now are enrolling some additional populations of children as well as adolescents and young adults to then target samples taken at four days after the second dose. Once we define the nature of the specificity of the troponins in this larger population, then we would use

that to inform how best to look at those troponins.

As of today, we don't have that data, and again, I want to be careful in those circumstances. I'm sure you can appreciate. We want to make sure we have enough specificity around this so that we don't end up having an erroneous result.

DR. CODY MEISSNER: But you can compare the two groups obviously?

DR. WILLIAM GRUBER: Right. Right. I mean, that's the idea that we basically -- once we have that specificity and know the incidence with which we're potentially seeing a spurious result, then we can better decide the nature of what the data would -- how the data would inform us from the troponins with the samples that we're getting to test in troponins in the vaccinated children.

DR. ARNOLD MONTO: Thank you. Very focused questions now. Dr. Gans? Only one-part question.

DR. HAYLEY GANS: Thanks. I had a question about the PRNTs (audio skip) our sponsor that were reported, and they were reported against the Delta

strain, variant, and obviously, we have previous data. So this was presented on the cohort that was studied for their clinical trial for the 5211. I'm wondering how that compares with the six-month data that we've already collected on other individuals so that we can start to understand how relevant that's going to be going.

Then were any of the new variants of concern tested even on an experimental basis? I realize these are new tests. Because some of those are going to start circulating.

DR. ARNOLD MONTO: That's the second part.

DR. HAYLEY GANS: Well, it's about variant (audio skip).

DR. ARNOLD MONTO: No, that's okay.

DR. WILLIAM GRUBER: Yeah. So let me answer the second part. We've not tested in the pediatric population, the responses to new variants. But you may recall from the discussions we had about the booster, not that long ago at an EUA, we described how across the board we've yet to find a variant that seems to

escape neutralization, and given -- again, let me just show Slide 1 just to remind ourselves of what we've seen with the Delta variant. Slide 1 up, please.

You can see here that we have very comparable responses for the wild type versus the Delta strain in the target population for this study, and we've shown much the same thing in the circumstance where we've looked adults. So, given this type of comparison, we would expect the same thing to apply. So whether it's the Delta variant or perhaps a variant in the future, we would expect good coverage so far.

DR. HAYLEY GANS: But these were done shortly after vaccinations, so I'm wondering how they compare with the ones that we saw previously (audio skip) level. So I'm looking at percent.

DR. WILLIAM GRUBER: Yes. I think the circumstance where we saw some decrease in efficacy was obviously in the circumstance where we were beginning to get into a circumstance that you've seen with the real-world evidence in the Delta variant phase. And although there was some drop in overall real-world

effectiveness, it was generally well-maintained, particularly for serious disease. And so we would expect the same thing. But again, we'll need to study this, and we'll be able to by virtue of having obtained the specimens and obviously looking at real-world evidence.

DR. ARNOLD MONTO: Two final questions, Dr. Nelson?

DR. MICHAEL NELSON: Thank you. I do believe this is a short one for the sponsor itself. Can you provide us with any additional insight into dose selection? So, very appropriately, the 10-microgram dose was chosen based on the (inaudible) immunogenicity and certainly the lowest reactogenicity. Were there any lower doses checked, or was there pre-clinical data suggesting that maybe lower doses would result in suboptimal humoral cell-mediated responses or perhaps even shorter durability of results?

DR. WILLIAM GRUBER: Yes. Thanks for that question. Maybe we can show Slide 1? Again, the details of how we went about dose ranging to some

extent are included in your briefing document. But you see here represented what we were looking at when we made the decision in Phase 1 to move forward with the 10-microgram dose, and that was based on coupling this information where you can see on the left-hand side, 10-microgram neutralizing antibody responses, as well as 20 micrograms.

First is what was seen in the 16- to 25-year-olds, which was ultimately, of course, going to be the comparison group for the non-inferiority trial. It was in this circumstance where we saw the 10 micrograms already was associated with a significant reduction potentially in reactions in the setting where it was already looking like it was going to exceed responses in 16- to 25-year-olds.

Now, mind you, take note of what's on the X-axis because this was seven days post-dose 2, and we know that's the peak after two doses, and then there's a decline within the first month. So we reckon that there would be some decline. We reckon we already had a good safety profile and that we would meet

noninferiority. As it turns out, we did.

So that's probably the best evidence that we chose the optimum dose because we're at a geometric mean ratio of 1.04 with a post hoc criteria from the FDA to try to meet that number with reactions that are below those for fever and chills and a number of symptoms compared to 1625. So we think we have optimized the immune response and minimized reactions.

DR. ARNOLD MONTO: Thank you. Dr. Kurilla, you've got the last word in the questions.

DR. MICHAEL KURILLA: Thank you. Thank you, Arnold. Yeah. One for the sponsor. I'm assuming that based on the data you've presented that you have no immunogenicity data just at the time of the second dose being given. I'm wondering whether there's any interest, or do you have anything ongoing that would maybe inform whether or not someone who has had a prior COVID infection can get by with a single dose.

The other question is, are you looking at different dosing intervals? Because the three-week dosing interval, quite frankly, seems to be suboptimal,

at least in terms of durability of the antibody response.

DR. ARNOLD MONTO: I was going to disallow the second part, but, since it's one of the questions I have, I will allow it.

DR. MICHAEL KURILLA: Thank you, Arnold.

DR. WILLIAM GRUBER: All right. So let me address the -- since both of you are interested in that last question. Obviously, at the time of the pandemic, we're trying to solve, first and foremost, for providing protection in a short interval of time, and that's why we were very pleased to be able to dose at a 21-day interval first in adults and then carry that over into the pediatric population.

Obviously, as we think farther ahead to a post-pandemic period, and particularly as we get into very younger populations, it may be advisable and probably will as we get particularly in that first year of life to look at longer intervals as part of a routine immunization series, but we don't have that data now.

Then the first question, we don't have data currently to describe on the immune responses after the first dose, but I think you can get some sense of what happened to adults after the first dose where we typically did not see neutralizing antibody, except potentially in the circumstance where individuals had prior exposure. But we reckon that, again, particularly given the importance of durability, that two doses are likely going to be required to essentially provide full protection.

DR. ARNOLD MONTO: Thank you and thank you to the sponsors and to FDA for their presentation.

COMMITTEE DISCUSSION AND VOTING

DR. ARNOLD MONTO: We're now moving into the general discussion leading up to the voting question. Could you, Mike, put up the voting question? It is our one and only discussion topic leading up to the vote. So I think it --

MR. MICHAEL KAWCZYNSKI: Yeah. Give me a

moment here.

DR. ARNOLD MONTO: Okay.

MR. MICHAEL KAWCZYNSKI: I'll put it back up in that sharing screen. We went back and forth.

DR. ARNOLD MONTO: All right.

MR. MICHAEL KAWCZYNSKI: We accidentally pulled it out. So I'll put it back up. You are looking for our community discussion, correct?

DR. ARNOLD MONTO: Well, this is a voting question. You can find the voting question --

MR. MICHAEL KAWCZYNSKI: Yeah. It'll be in there. It's in there.

DR. ARNOLD MONTO: Okay.

MR. MICHAEL KAWCZYNSKI: So I'll pull it up right now.

DR. ARNOLD MONTO: Whatever it is (inaudible) that has it.

MR. MICHAEL KAWCZYNSKI: No problem. Coming in now. All right. There it is. So, let me just stop touching the slide.

DR. ARNOLD MONTO: There it is. Okay.

MR. MICHAEL KAWCZYNSKI: There we go.

DR. ARNOLD MONTO: Now we won't have to read it out to you. You can all read the voting question, and this is what we are going to be discussing. This is the overall voting question we're going to have to vote on in a couple of hours or less than a couple of hours since we've cut into the discussion time.

As a question of process, what we will do is conclude the discussion. We will have the vote, and then for anyone who wants to explain their vote, there will be time to discuss and explain the vote. So you can talk about the voting question and should talk about the voting question as we go through the discussion, but there will be additional time for those who want to explain their vote. It's not mandatory, but available. Okay. So Dr. Gans, are you up again?

DR. HAYLEY GANS: Thank you so much. I'll just open up, I guess, this conversation with a couple of points. For me, there's very intriguing data to -- regarding the disparities that we've seen in terms of COVID disease and outcomes. For that, I think it's

very impressive that we need to provide some safety net that isn't available otherwise without vaccination and prevention of some of the outcomes we've seen.

I think very importantly are some of the learning loss outcomes, not only as it would pertain to loss of school time, which we know is very real in many children's lives, but also in terms of outcomes and so there's data that is being collected on memory loss and other things as it relates to really the outcomes of COVID disease and trying to prevent further loss in these children.

The other things that I think are really important for us to understand as we're moving forward is that it's probably in this age group of people have identified over analysis of the outcomes in terms of the one thing that we're sort of looking at because it was seen in the older children of the myocarditis or any of the cardiac effects because those rates are lower in this group anyway and the doses used here are actually lower and more appropriate for these age groups.

So I think those are important points for conversation and I think for understanding what is before us.

DR. ARNOLD MONTO: Thank you. Very good opening to get us on track. Dr. Levy.

DR. OFER LEVY: Yeah. This has been a fascinating day, and I'd like to thank FDA and the sponsor and CDC and everyone for a very thoughtful discussion. There were a number of broad-based principles here that are converging. One of them was touched on by Dr. Gans, which is the concept of including children.

In fact, there's something called the pediatric research initiative, or PRI, that was passed on the federal level to include children in biomedical research, and we're happy to see that studies are being done because this pandemic is clearly affecting them both directly and indirectly as we've heard today. So I very much welcome these data, and in many ways, they're promising.

Still, the challenge we face based on the

question that we're confronted with now with Committee members is that the risk-benefit or benefit-risk analysis and FDA has taken great effort and presented to us today and taken a lot of questions about these different models, and we see that we can reach different conclusions to some extent based on the assumptions that the models are built on.

One of the factors, of course, is how much coronavirus is circulating in a community at a given point in time and then other factors as well. What will the actual myocarditis rate be in these younger kids who may be less susceptible to myocarditis? But right now, that's a speculation. We don't know that for sure, and the studies were empowered really to answer that question in the 5- to 11-year-olds.

So I'm just pointing out some broad-based themes that are running through my mind as we're having this conversation. It's a very meaningful one. I also am wondering whether the prevailing conditions could somehow work their way into our recommendations because after all, that's the spirit of an EUA. It's

authorized in the setting of a public health emergency, which we're in now, but one that is fluid. So I'm going to leave my comments there, but I hope they're helpful. Thank you, Dr. Monto.

DR. ARNOLD MONTO: Yes. Very helpful because we are in a fluid situation, and that's why it's a good thing we've got an emergency use authorization and not an amendment or anything like that to do the license. We are confronted with a binary choice as indicated in the voting question. Keep that in mind as we move ahead to Dr. Rubin.

DR. ERIC RUBIN: Thanks, Mr. Monto. This is a much tougher one, I think, than we had expected coming into it. Data show that the vaccine works and is pretty safe, at least by immunobridging and even by some real-world clinical data. Yeah, we're worried about all of these -- we're worried about a side effect that we can't measure yet, but it is probably real. We see a benefit that isn't the same as it is in older age groups.

So, for me, I think it's going to revolve

around two questions. First off, whether there is going to be a use for this vaccine in this age group, and then how the decision gets made to use it within this age group. I think what sways me here is that it's a very sort of personal choice. If I had a child who was a transplant recipient, I would really want to be able to use a vaccine like this. There are certainly kids who probably should be vaccinated.

The question of how broadly to use it though, I think, is a substantial one. I know it's not our question, and I know we're kind of punting that to ACIP, but I do think that it's a relatively close call. And, as Dr. Levy just said, as Dr. Gans said, it really is going to be a question of what the prevailing conditions are.

We're never going to learn about how safe this vaccine is unless we start giving it. That's just the way it goes. That's how we found out about rare complications of other vaccines, like the rotavirus vaccine. I do think that we are going to -- I do think we should vote to approve it.

DR. ARNOLD MONTO: Thank you. Dr. Hildreth?

DR. JAMES HILDRETH: Thank you, Dr. Monto. Well, I have several thoughts here. One of the things that's really been impactful for me is to learn that the prevalence in children might already be 42 percent, which means that 30 million of the 72 million children in our country, they have some form of immunity to the virus already.

The other thing is that I was disappointed that the number of minorities in the Pfizer study got such a small percentage of the total because they bear the brunt of the disease and hospitalizations. It just seemed to me that in some ways, we're vaccinating children to protect the adults, and it should be the other way around, that if 30 million children already have some form of immunity, they've made their contribution to herd immunity already, and our focus should be to get the adults vaccinated to protect the children.

So this is a really tough one for me, but I do believe that children at highest risk do need to be

vaccinated but vaccinating all of the children to achieve that just seems a bit much for me. So I'm having some challenges with this one. Those are my thoughts, Dr. Monto. Thank you.

DR. ARNOLD MONTO: Dr. Sawyer?

DR. MARK SAWYER: So I do -- we're all concerned about the myocarditis issue, and I do think the model has overestimated the hospitalizations prevented because of prior immunity and the inclusion of some kids who are hospitalized for reasons other than COVID. I also think the high estimate of myocarditis is probably too conservative based on the natural history of myocarditis generally being less common in this age group.

I'll paraphrase Dr. Fauchi who said models are what you rely on until you get the data, and then you throw out the model. So the models are the best we have at the moment. As was just mentioned, we are not going to get the data unless we start to use this vaccine.

I do think we need it as a tool in our

armamentarium for high-risk children for equity issues, for parents who really would like to protect their children and because of the long-term, very profound implications of schools being disrupted and the social and educational impact that that's having.

So I agree that it's going to be a fluid situation. A reminder that an EUA is not a permanent situation, and that could change based on either additional side effect data or depending on what happens with the pandemic.

DR. ARNOLD MONTO: Thank you. Dr. Offit?

DR. PAUL OFFIT: Thank you, Dr. Monto. So I guess for me, it's always nerve-wracking. I think when you're asked to make a decision for millions of children based on studies of only a few thousand children. So I mean, I guess the way I struggle are us trying to deal with this is that it's never one you know everything, you never know everything. The question is, when do you know enough.

I think we certainly know that there are many children between 5 and 11 years of age who are

susceptible to this disease who could very well be sickened or hospitalized or die from it. Then regarding the myocarditis issue, I think there were a number of things that are reassuring. It is reassuring to me that we're giving a lower dose.

It's reassuring that the incidence of myocarditis in a 12- to 15-year-old is less than that in the 16- to 29-year-old and that at least the general classified myocarditis is not generally a phenomenon of the prepubertal child, or at least much less so. We do have efficacy data at 91 percent. I think that will hold up. So I guess for me, I think I know enough to move forward with a yes vote. It's always never when you know everything; it's when you know enough. So thank you.

DR. ARNOLD MONTO: Right. And it's a binary choice that's put in front of us, which is always difficult. Dr. Portnoy?

DR. JAY PORTNOY: Thank you for the discussion and the opportunity to say this. Technically, I'm the consumer representative, and I've had over 4,000 emails

from consumers asking me to vote no. Thank you for those, but I feel like I need to also represent the consumers' parents that I see every day in the clinic who are terrified of sending their children to school because they're not protected against COVID.

There's all this anti-mask rhetoric, parents who don't want to get vaccines. Parents are just terrified of sending their kids to school, and I feel that they need a voice also because they're not being represented. I've looked at the data, and I'm going to use the data when making my decision because I think that's what we have to do is to look at the cost and the benefit of this vaccine.

I really appreciate the benefit and the risk analysis that was done. It's extremely informative. It really helps to center it. So I think that this virus is just the beginning. Our kids are going to be dealing with this virus for many years to come. It's going to come repeatedly and getting this vaccine is just the first step that they're going to take towards being able to protect themselves from getting this

virus and having bad outcomes.

And so I really appreciate the opportunity to participate in this activity. I think that the information has been extremely helpful, but I think that the evidence is pretty clear that this vaccine is worthwhile. Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Lee? And please, members, check to see whether you still have your hands raised.

DR. JEANNETTE LEE: So I would say I kind of agree with Dr. Offit of how much -- do you know enough? I would say that I was really sort of impressed with the efficacy data, the immunobridging data. Obviously, the adverse events are always a concern, but they don't seem to be overwhelming really at this point. I will say that the school closures and the disruption, I think, has been enormous, and I think that we have to weigh that against the benefits that we would see for the vaccine.

I definitely think the benefits outweigh that. But, obviously, we'll have to follow these kids for

some time to see how that happens. I mean, the reality is, I think, at one point we thought if we vaccinated enough people that the virus would go away. It's not going away, and I think we're going to have to find a way to live with it, and I think the vaccines kind of give us a way to do that. Thanks.

DR. ARNOLD MONTO: Thank you. Dr. Gans. We see you. We don't hear you.

DR. HAYLEY GANS: Yes. Yes, thank you.

DR. ARNOLD MONTO: Okay.

DR. HAYLEY GANS: As I was listening to my colleagues, I greatly appreciate their viewpoints. I just wanted to bring up one additional thought that hasn't been raised. The current rates are still within a great deal of mitigation for some of our populations, most of our populations. We really can't continue to do that.

The other thing that we have to realize is we actually have to open back up. And, in order to do so, we actually need to provide a way of allowing individuals who are interested in preventive measures

and protecting individuals from actually seeing disease, which again, even in asymptomatic individuals who have experienced this disease, there are outcomes that one would not necessarily want for their children.

So we do need to think about that and think about the fact that we can't forever have mitigation particularly in schools and children need to learn in the more open life as we all do. So that's an important thing to remember as we're considering those models and rates that we're seeing in those models. Those are with mitigation (audio skip) so it's important to remember that it likely will go up and we're heading into (audio skip).

DR. ARNOLD MONTO: Dr. Pergam?

DR. STEVEN PERGAM: Thanks, Dr. Monto. A really great discussion by colleagues. I think the thing that continues to stick in my head is, I'm trying to put myself in the position of a parent who has a child that's at particular risk, whether it's obesity, whether it's immunocompromised position, lung disease, that currently does not have the option to give their

children this vaccine.

Depending on how the ACIP votes on this, this vote will really affect whether they can protect their children. Those are kids that are being held out of schools because masks are not being used in all locations. I think we have to think beyond how this would be used as a general group, but also to think about those who are potentially at highest risk. I think that's going to affect how I'm thinking about this position to vote.

DR. ARNOLD MONTO: Dr. Kurilla?

DR. MICHAEL KURILLA: Thank you, Arnold. Yeah. So, like my colleagues, I think this is probably the toughest decision. I'll be honest and say I actually resented this sort of binary presentation. It's sort of like a take it or leave it. You must have everything exactly the way the sponsor has presented it and nothing else can be considered.

A few thoughts. The argument in favor of that this will lead to herd immunity and a reduced transmission, that's a theoretical possibility. I've

seen very little data. And in fact, most of what I see right now is that regardless of the percentage in terms of vaccination that the newer variants seem to be able to pass through the population. So, if all we're focused on is reducing cases in terms of a benefit, I don't think that's likely to be realized.

I have a lot of issues with the immunobridging because it's being based on an immunogenicity marker that we know wanes and yet, continues in spite of the waning of that antibody response, we continue to see very good protection against the very things we want to see protection against, hospitalizations, severe disease, death.

But we're making an assumption that at a lower dose in this pediatric population that it's just going to pass -- that there's going to be equivalency in terms of the overall protection because of the antibody response.

So I have a lot of issues with that, and particularly with the percentage of the population that has already been infected previously with COVID, and I

think 40 percent is probably a lower limit. I think the possibility that they likely only need one dose at best is going to be very optimal, is probably going to be more than sufficient for them.

So I think the idea of doing it under an emergency use authorization two dose for everybody without any flexibility around this, I think is going to just not go over very well, and I don't think it's going to give the healthcare community the options and parents the options to choose what's best for their children. There are high-risk individuals, and I think they do need to be attended to, that we do need to provide a vaccine for them, but, for many others, one dose or no dose, even if they've had prior COVID infection, I think they may not need anything more.

The last point I would make is that we are vaccinating with a prototype spike protein that is no longer circulating. So we have to go to higher and higher levels in order to get efficient potency in terms of neutralization. Everyone is focused on Delta right now, but Delta is on the decline. We can

anticipate that the future variants are going to be more distantly related and simply boosting, which we're likely to need to do in this population in six months if all we're relying on is neutralizing titers, is going to become harder and harder to do.

So I think there are -- we need to more carefully evaluate exactly the vaccination schemes that we want going forward, and we simply don't have the data right now to make those decisions.

DR. ARNOLD MONTO: Thank you. Dr. Levy?

DR. OFER LEVY: Yeah. I have another comment that relates to how Dr. Marks framed our discussion today. He was clear to say, "Look, our purpose today is not to decide who exactly receives it within this age range. Our purpose today as the VRBPAC Committee is not to discuss or consider or consider mandates." That's true, of course. Technically, that's not our job right now.

Nevertheless, I'll speak for myself, and I highly suspect the other Committee members as well. We have in the back of our minds that after our vote how

this is used. This goes on -- could go on later on to CDC depending on outcome and how it's implemented across states and counties can vary, and we're hearing from some of the Committee members some sympathy to the view that, well, maybe it's good to make this available to certain families, children at higher risk, comorbidities.

There have been a number of publications around comorbidities related to severe COVID in this age group -- obesity, asthma, other conditions, immunocompromised, et cetera -- and is that an option? Typically, FDA wants us to vote on the question yes or no, Dr. Monto, as you told us as phrased. But is there the possibility, also, of considering rephrasing? We've certainly done that as a Committee recently. So, I just wanted to share that thinking. Thank you.

DR. ARNOLD MONTO: Dr. Marks, can I ask you about this? In front of us, we have a binary choice. That is the question for today.

DR. PETER MARKS: Yeah. I appreciate the Committee's discussion very much here. I also

appreciate the fact that we did not present today the emerging epidemiology of COVID across the globe, including what's been happening with increases in Europe and other areas and other concerns.

I would ask that we first vote on this question, and then once have a vote on this question, we can make a determination thereafter if we vote on -- if the Committee would like to explain their votes, ask for something else, we could potentially either poll the Committee or vote on something else. But I think it would be helpful to have a vote on this question.

DR. ARNOLD MONTO: It was my understanding this is the question for today. Is that the case?

DR. PETER MARKS: That is the case.

DR. ARNOLD MONTO: That is the case. Okay. Let's see. Dr. Meissner?

DR. CODY MEISSNER: Thank you, Dr. Monto. An awful lot has been said that's very, very interesting and that I agree with, and I'd like to make a few comments. I think the likelihood that this vaccine is going to be effective is pretty likely in that the 6-

to 11-year-old age group. The issue is side effects or adverse events that might be occurring after this vaccine. I'm torn.

On one hand, we know that many mothers and fathers and parents are eager to administer this vaccine to children because they're so frightened, perhaps overly so. They're so nervous about this vaccine because of what's been stated that they really are anticipating having access to this vaccine in children.

On the other hand, I think we saw that approximately 68 percent of the children who are hospitalized with COVID-19 have underlying comorbidities. So, that means about 32 percent do not. Then, if we were to take 40 percent of that group that may have immunity already, we're getting down to a very small percent of otherwise healthy 6- to 11-year-old children who might derive some benefit, and we simply don't know what the side effects are going to be.

For example, it's not even clear that this vaccine will reduce rates of transmission. We're

hoping that's the case, but we don't know. This vaccine is probably not going to prevent infection. It's going to prevent severe disease. So, my worry is that -- I think my thought is that this vaccine should be available to those parents who are very eager to get it for their child and because their child has a comorbidity, or they're concerned themselves.

I'm just worried that, if we say yes, that the states are going to mandate the administration of this vaccine to children in order to go to school, and I do not agree with that. I think that would be an error at this time until we get more information about the safety. So I think I agree with what everyone is saying here. We're in a very difficult decision-making process.

DR. ARNOLD MONTO: Dr. Marks, can I ask you to help us a little bit because we are hearing some reservations about use? Also, the question of how various groups that we have no control over will further act.

Yet, if we do not approve, we will be denying

the vaccine to families that have a vulnerable member present and who have been keeping their kids in because they're concerned about infecting that individual, we will be denying the vaccine to others who, for one reason or another, want their child to be protected or a risk, which we cannot really accurately estimate for all the reasons we've heard up to now.

Help us out in terms of, if we vote yes, what happens? Clearly, if we vote no, then the vaccine will not be available to anyone. You're muted.

DR. PETER MARKS: Sorry. Double muted. Thanks very much to the Committee and thanks for the very thoughtful deliberations here. I just want to -- and before I get to answer that question, just remember here, also, that we take measures to prevent influenza in children in order to prevent about a hundred deaths a year from influenza, and we're talking about having this become more of a routine type of thing. So just so we understand the order of what we're dealing with.

The other issue that I would just bring up here is the issue of vaccine equity and that, if we try

to approve this for some subset of the group, that that could potentially lead to a situation where this becomes a vaccine that gets used more in those who are of a socioeconomic status that they're able to maneuver to receive the vaccine. That would put some at disadvantage.

So, I think we just need to be careful about where we go with that. At the end of the day, the way this process has been set up is that it's this body's decision to make sure that the data supports the safety and effectiveness and that the Advisory Committee on immunization practices then discusses the deployment of the vaccine. I would suggest that we take a vote on the question as it's written, and then, if the vote fails, then we can tailor the vote to a subpopulation at that point.

DR. ARNOLD MONTO: You feel -- okay. Let's move on to -- since you mentioned ACIP, let's move on to Dr. Cohn.

CAPT. AMANDA COHN: Hi. So, I'm reflecting a little bit on the challenging discussion that we're

having as a Committee, and I think part of the problem is that we're now talking about children. When we are talking about children, we both don't accept deaths and severe outcomes in the same way that maybe we accept to some degree in older age groups, but we also don't accept risks.

I guess, when I look at this question, it is pretty clear to me that the benefits do outweigh the risk when I hear about children who are being put in the ICU, who are having long-term outcomes after their COVID, and children are dying. As Dr. Marks just said, we vaccinate routinely against several vaccine-preventable diseases for which far fewer deaths and hospitalizations and ICU admissions occur.

So, to me, the benefit is clear, even beyond the direct benefit and the personal experience that I know we're all having with children in our lives who aren't able to go to school. So, then when I look at the risk side of it, I see that the children in the clinical trial, it's not substantially lower than other clinical trials for vaccine-preventable diseases, which

have evaluated the safety, and we have this known rare adverse event of myocarditis in an older age group with a different formulation of the vaccine.

So, while I would not -- I don't want to minimize the risk. I do think that you -- that we could -- at this moment based on the totality of the evidence, the benefits do outweigh the risk and as this vaccine is used, which I think has been said before, we have incredible safety systems in place to monitor the potential for myocarditis in this age group, and we can respond quickly as we've shown, we've done it for every other rare adverse event that our safety systems have identified.

So, to me, the question is pretty clear. We don't want children to be dying of COVID, even if it is far fewer children than adults and we don't want them in the ICU.

DR. ARNOLD MONTO: Thank you. Dr. Lee?

DR. JEANNETTE LEE: Sorry. I needed to lower my hand. Sorry.

DR. ARNOLD MONTO: Okay. Dr. Fuller?

DR. OVETA FULLER: Thank you, Arnold. So, I want to -- I actually appreciate this question being phrased the way it is. I'm not going to turn my camera on for broadband purposes, but my question -- and I agree with what Dr. Cohn just said, that the long-term risk -- if I were a parent of a child in this age group, I would want to have the choice. We can't have the choice unless the vaccine is available.

So, rather than only the high-risk children, and the question becomes, how do we know the risk for any child, and how does the parent make that decision? So, would Dr. Marks or someone remind me, please, of the pharmacovigilant processes that will be done to pick up things that that may not have shown up in the children in the trial, but as a parent who's considering this for my child, how will I know as it rolls out in the real world if there's something that does show up?

I know we have those. Just remind me and everyone listening what those are so that we can feel confident that should something come up, it will be

detected. I believe that's what happens, but just remind me, please. Because I think, if we don't make it available, we will never know what will happen with a larger group of people. So, I just ask that of Dr. Marks or maybe Dr. Cohn or someone who has that sort of information, please.

DR. PETER MARKS: Dr. Fuller, thanks for that question. I will start, and then if Dr. Forshee or someone wants to jump in to augment what I'll say. What we have done during this pandemic is we have an overlapping safety surveillance system that is done in collaboration with the Center for Disease Control and Prevention, so FDA and CDC share this responsibility. There is passive safety reporting as we've heard about today multiple times through the Vaccine Adverse Event Reporting System.

Moreover, there's active safety surveillance, which is done by the CDC system using the vaccine safety datalink, which has about, I think, 14 million lives covered to be able to look in near real-time at events that are coming up and then we have the Sentinel

BEST system, which is what we've done, used to evaluate myocarditis in about 20 million vaccine recipients. So, and that's even a larger system that continues to grow.

So, we will continue to actively look for adverse events, and I think the important thing here is to say that the safety teams at -- and I can speak for this in this case for CDC because I know them and at an FDA -- are incredibly committed and devoted to making sure that we understand the nature of the safety events and then we catch these signals as soon as we possibly can. So, that's what we're here to do. Does anyone from my team or CDC want to add into that? You're muted, Rich.

DR. RICHARD FORSHEE: Thank you very much, Dr. Marks. This is Rich Forshee. I just wanted to quantify a little bit what Peter said in terms of the BEST system that we have in place, as Dr. Wong said in her presentation earlier today. That covers somewhere between about 25 percent to 30 percent of the people in these age groups depending on which specific cut you're

looking at.

So, we have a substantial percentage of the pediatric population that's included in our biologic spectrum that's in safety system that we can use to monitor for myocarditis or any other potential adverse events that may come up. Thank you.

DR. OVETA FULLER: Just a quick follow-up in this. I have a child that I get vaccinated, and I'm really concerned about something happening with him or her, I can go to my primary physician who then will either comfort me or tell me I haven't seen that. They will be basing that decision on what you are looking at in those databases. I guess the question is, how likely is something to get past or ignored by you?

I think that's been a lot of the questions that have come up from other people. It's like all these things are happening, but we have no data for that. Are we missing it, or is there other things happening that have nothing to do with the vaccine but may just be coincidental? So, how would I as a parent be comforted by the fact that I know I have a system

that is going to allow me to pick up on anything that may be vaccine related.

DR. RICHARD FORSHEE: Yeah. Thank you. Go ahead, Dr. Marks.

DR. PETER MARKS: Let me start by this, and then I'll pass it over to Dr. Forshee. Obviously, it's very challenging to figure out whether there are emerging -- what an emerging safety signal is. It is easiest when something is very unusual because it didn't take very many cases of thrombosis or thrombocytopenia syndrome to be able to pick that up.

We also are able to pick up things like Guillain-Barre syndrome, but these systems do a -- our statisticians are constantly looking at -- at this point, I think it's 16 potential adverse events of interest, and I'll let Dr. Forshee say more about that. Those are events that have been seen with other vaccines. In order to look for things that might come up and then understand whether they are at a higher rate with the vaccine than without. Rich, maybe I'll pass it over to you to describe that more.

DR. RICHARD FORSHEE: Thank you, Dr. Marks. So, I just want to build on what Dr. Marks said earlier about the systems approach that we have here. The vaccine adverse event reporting system is particularly good at catching early, unexpected safety signals that we may see. The BEST system and BFC provide us with systems that are more robust in terms of conducting statistical analyses.

One thing to keep in mind, however, is that there is some lag with events appearing in these data systems. Claims have to be filed. Claims have to be made available in the data analysis files that we have. So, we do have a robust system, and it has different components to perform different functions. I think I'll leave it there. Thank you.

DR. OVETA FULLER: All right. Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Cohn, and when you're done talking about the systems, could you also talk about what ACIP would do with the recommendations because I think we don't want to overlap the role of ACIP in fine-tuning the approvals

that we give and that the ACIP gives because I think that's where I'm afraid we may be going in that direction right now.

CAPT. AMANDA COHN: Sure. So, the first thing I'll say is that whenever I -- we hear the parents whose kids had medical events that occurred near the timing of a vaccine, and it is really, really hard when something devastating happens to your child, and you want so badly to try to understand what's happened. When a vaccine has occurred in that time frame, it can be very -- I can see how easy it would be to connect the vaccine with the adverse event. So, I definitely don't want to diminish the way that any parent feels.

However, we do have several systems in addition to what was just described. We also have CISA, which is the Clinical Investigation Safety team for which a physician can call on at any time, and they have done dozens, if not, hundreds of clinical consults over the past -- I guess, over the past ten months to evaluate potential of an adverse event that is even so rare that it wouldn't be picked up in our safety

systems being connected or related to the vaccine.

So, this is what has allowed us to really review some of these very rare adverse events and to look at them and to try to, first of all, find another reason for that event to have occurred, which sometimes nobody is able to do. So, you can't completely rule out the possibility of a rare adverse event.

That being said, the combination of the safety systems, especially as Dr. Marks was saying, in the setting of a rare -- an event that occurs very rarely in a population, such as myocarditis in these 5- to 11-year-olds or any of the other adverse events that have been detected. When we say we look at these 16 or 20 conditions regularly, it's called rapid cycle analysis. The point of that is to look nearly every day at whether or not these signals are being detected in our active surveillance systems.

So, parents have the opportunity to enroll their child -- they will have the opportunity to enroll their child in V-safe and report symptoms and report medical events. We have this group of experts to help

support clinical decision-making for providers who see rare adverse events or concerns about an adverse event that's related to a vaccine and in addition to our large safety databases that we look at regularly.

In terms of HAP, I'd like to say that FDA has the regularity decision-making over whether or not a vaccine or another product is safe and effective and can be used. The ACIP then takes those considerations of use or that indication that FDA makes and looks at other variables beyond just safety and effectiveness to look at who would benefit from the vaccine and what -- who should get vaccinated.

So, that includes things like equity, feasibility the indirect burden that we've talked about from today. So, they look at the totality of the evidence and don't just focus -- while safety and effectiveness is an important component of that, they look at potential impact of recommendations on a population. So, I think -- if that helps clarify the difference, I think that -- I can answer any other questions.

DR. ARNOLD MONTO: What I'm really trying to get at is a more broad approval or a more restrictive approval because that is not traditionally what is done in FDA during approvals. So, you're talking about population groups to receive the vaccine. how would our discussion that we are having right now impact -- I know you can't predict, but how would that impact the ACIP discussions?

CAPT. AMANDA COHN: Sure. So, if the FDA limits an authorization to a population, as you saw with the booster dose recommendations for the mRNA vaccines, based on VRBPAC feedback, then ACIP could not go beyond those conditions of use. So ACIP could limit further, but they can't make the decision to expand the (inaudible).

DR. ARNOLD MONTO: But they can limit?

DR. AMANDA COHN: They can limit further. So, if FDA authorizes a product more broadly, then ACIP can look at which specific populations may benefit and will benefit from the vaccine and can make more focused or nuanced recommendations if they choose, or they can

recommend that the entire population that FDA authorized the product for is recommended to receive it as you saw in December when we recommended all individuals over the age of 16 or 18 be vaccinated.

DR. ARNOLD MONTO: Thank you, Dr. Cohn. Very helpful. Dr. Levy?

DR. OFER LEVY: Sorry, that is an error. Please go to the next.

DR. ARNOLD MONTO: Okay. Dr. Perlman?

DR. STANLEY PERLMAN: Yes. So, after listening to all this discussion and thinking about the ACIP, I'm going to vote in favor of this. (Audio skip)

MR. MICHAEL KAWCZYNSKI: We don't want to have anybody thinking. So, all right. So, again, thank you. We were holding off until -- we want to make sure -- we're just going to make a quick announcement that we do have some widespread power outages. So, we want to make sure we didn't miss anything with Dr. Perlman. So, now that we're reconnected, Dr. Perlman, take it away with your question.

DR. STANLEY PERLMAN: Okay.

DR. ARNOLD MONTO: Please start from the beginning.

DR. STANLEY PERLMAN: Okay. I'll see if I can repeat that.

DR. ARNOLD MONTO: If you can try.

DR. STANLEY PERLMAN: Yeah. If I can remember what I said, right. So, I was just going to say that I'm going to vote in favor of this question. As I've listened to all the discussion, all of which I basically agree with, it occurs to me that not only are we talking about acute disease, but we're also talking about the other things that Amanda talked about, the effects on families and transmissions to other people. Then also, along COVID, which may be the biggest problem that we have, certainly in adult populations, maybe in pediatric populations.

So, I would want to give families the options of getting their children vaccinated if they choose to. The other thing is that even the shedding scenes are so important for transmission. We don't really have data that there is an effect on shedding, but, based on

other studies and other coronaviruses and even to animal studies, it's likely that we will see an effect on shedding. The problem with shedding is that we almost have to do the transmission study to see if people in the household get infected.

There may be virus left in the nasal cavity after a vaccine, but the question is, is the shedding is longer, the levels is high, and I think that we don't really have very good data on that. I think it's so important as it's been mentioned many times in this discussion.

The final thing is that one of the things we -- reasons we care so much about the risk-benefit ratios is I think it's really been hard finding much of a risk. Much of it so far has been more based on older populations. So, I think the analyses that were done by the CDC were great. But part of the issue is that so far, the risk has not been very high in what we've seen.

DR. ARNOLD MONTO: Thank you. Dr. Moore?

DR. PATRICK MOORE: Thank you. So, I found

the Committee discussion on this really, really thoughtful. The way I'm thinking about this is that there were -- what are the facts? We do know that there were 94 children in this age group who died of COVID. They all have names. All of them had mothers, and these kids died of COVID.

In contrast, we're worried because we -- this group has not been vaccinated before, we're very worried about a side effect which is real. It cannot be dismissed, but, on top of that, we're extrapolating from higher risk boys and men in older age groups, the side effect from a higher dose vaccine, and that's a theoretical risk. It's an important one. Fortunately, no one has died from that that fits that profile.

Now, if the surveillance systems do start seeing severe outcomes and deaths from vaccination, I'm quite confident that those surveillance systems will tell us that we need to pause like we did with the J&J vaccine to really have a good idea of what the effects are of vaccinating this age group if we see that.

Two, it's also very hard for me to believe

that the risk for a severe outcome is going to come close to the known risk that we've seen for this virus in this age group, and to lay on top of that, thousands of kids that have been hospitalized, some of them, no doubt, disabled from that on top of the external costs to parents, to society, to schools, and so forth. So, to me, it seems like it's a hard decision but a clear one. Just want to throw that out.

DR. ARNOLD MONTO: Thank you very much. Dr. Pergam?

DR. STEVEN PERGAM: Yes. I keep coming back to the thought that we're in a different situation than we were before in the sense that one of the biggest concerns and where there's a lot of hand wringing about this is the issue of -- a question of myocarditis. We didn't know about myocarditis when we talked about this initially in the younger age group. We sort of learned about this process through this becoming utilized much more commonly.

I think we're going to be very tightly following this. I think the guidelines that have been

set up by the FDA for pharmacovigilance are specifically focused on this and other known outcomes. And, to me, it feels like that's a really different situation than we've been in when we've gone into populations with basically no knowledge, and I think we have this sort of warning.

I think, again, I keep thinking about what Amanda said -- that Dr. Cohn -- specifically about what pediatricians are going through and seeing children dying of a disease that potentially could be preventable and that, when we look at this data, the data we have in front of us says that it can be quite protective for individuals looking at antibody levels as well as even some of the outcome data.

So, I think it's really important for us to be thinking about this as we vote, and as well also recognizing that some of the decisions about how this was going to be used are somewhat out of our hands in what happens in the communities and with the ACIP and we should be voting on the question in front of us and not trying to interpret what will happen with the data.

DR. ARNOLD MONTO: Thank you. Dr. Kurilla? We have two more who are raised, and then we vote. Dr. Kurilla?

DR. MICHAEL KURILLA: It looks like the camera has burned out again. Yeah. I just wanted to make a couple of additional comments. There's a lot of talk about risks, and I think it's mostly been focused on the myocarditis and that's appropriate, but I think one of the other issues that's not discussed that much is when you're doing a risk-benefit analysis, you have to look at the benefit. And, while the benefit here is assumed to be prevention of severe disease, which is what we're all hoping for, one concern I have is that, particularly for that population of children that has experienced the previous infection -- which CDC estimates is 40 percent of this population which I think is probably a floor; I think it may actually be higher than that -- the question really becomes, does this vaccine offer any benefits to them at all?

Are they actually very well protected, and the other aspect here is for children who have undergone,

for example, a Delta infection, does now vaccinating them with a strain that goes back almost two years from the vaccine there from the time they're getting the vaccine, does that actually help or hurt their current immune system with regard to ongoing variants? I don't think we know that. We have no idea.

I think for many children who have experienced COVID already, they're probably more than adequately protected. One dose may be sufficient. I think for the high-risk children, it's very different, but I will emphasize again that this dosing interval, the way it was put together, is suboptimal in terms of durability. I think that there can't be any expectation that the antibody decay rate is going to look any different from the adults.

Then these children are going to be expected to have a booster in another six months, and I think the focus on cases, reducing cases, is really what's going to confound us because I don't think we're going to be able to do that. We're going to see vaccine breakthroughs in this population, and it's going to

cause all the same problems that COVID does whether or not they're vaccinated.

So, I think that we need to be a little more -- we have to have a little more flexibility in how this is implemented rather than add a single dosing primary vaccination scheme that is one size fits all.

DR. ARNOLD MONTO: Dr. Nelson?

DR. MICHAEL NELSON: Thank you, Dr. Monto. I understand why the question was asked the way it was, but I certainly don't like it. Accordingly, almost every vote casted today is probably going to be caveated based on the discussion we've had today.

Personally, I see this as an access and really a personal choice and equity question and not a mandate for all in this age group. It had to come to that decision, but certainly, that's where I centered, and we'll probably be in favor of this particular question.

To me, we should certainly not underestimate the knowledge and decision-making power of the public as evidenced by the open public hearing comments today, that content as well as, frankly, thousands of emails

some of us have received in the last couple of days. Providing choice to a fully risk-informed public using a shared decision-making model with their trusted providers, to me, is a pretty reasonable way ahead.

There are millions of at-risk children, and secondarily, family members needing risk-informed access to this vaccine for this age group. Unfortunately, I agree with Dr. Kurilla and the others who were discussing the impact of prior infection and probable existing immunity. Most families in the U.S. are flying blind with respect to their individual status.

So, in the absence of a testing strategy or having that knowledge, I think we're stuck with where we are and having to provide at least access to the vaccine and giving families the choice to make that vaccination. So, to me, depriving access to those with the highest risk could have some very devastating effects and hospitalizations and deaths that we'll resolve.

So, I deeply appreciate the thoughtful

approach that the Committee has taken thus far and the deliberation, I'll probably be supportive.

DR. ARNOLD MONTO: Thank you very much. Last word to Dr. Fuller, please.

DR. OVETA FULLER: Thank you, Dr. Monto. I'm just reminded from my infectious disease teaching that we have had vaccines for children before. I'm reminded of the polio vaccine campaign and Dr. Monto, you might actually remember more, that people and children could actually see the effects of polio on their classmates. We cannot see the effects of COVID-19 so dramatically on children, and thus, it weighs the question. Is it worth the risk?

I certainly believe that in hindsight who can look back on this decision giving parents the option to make that decision for themselves will be something that, in history, we will be glad that we were able to do and to look at the risk-benefit ratio and say that the benefits of this option far outweigh the known risk. We can't see the disease, but we certainly cannot anticipate all the risks ahead, but we have

systems in place that can help us do that.

So, I think we have to take a step and say we want to make this option available for what it might do to help the children as well as others in this pandemic. Thank you.

DR. ARNOLD MONTO: Thank you, Dr. Fuller. So, now we come to our vote. After the vote, we will have for anyone who wants to talk about why they voted and the caveats that are attached to their vote, we will have a chance for anyone who wants to do that to do so. Now, I think I have to read it for the record. Is that correct, Kathleen?

MS. KATHLEEN HAYES: Yes, that is correct.

DR. ARNOLD MONTO: Okay. For the record, "Based on the totality of scientific evidence available, do the benefits of the Pfizer-BioNTech COVID-19 vaccine when administered as a two-dose series, 10 micrograms each dose, three weeks apart, outweigh its risks for use in children 5 to 11 years of age?"

MS. KATHLEEN HAYES: Thank you, Dr. Monto, for

reading that aloud and just to provide some guidance before we bring up the voting poll. We do have 18 voting members today and 1 nonvoting industry representative attending the meeting. So, only these 18 voting members, excluding the industry representative, that's seen on this slide should be voting. If you are not an official voting member, please refrain as your vote will not be counted.

In regard to the voting process, Dr. Monto already read the question aloud for the record. So, all of the members and temporary voting members will cast their vote by selecting one of the voting options, yes, no, or abstain. You'll have two minutes to cast your vote, and once all of the votes have been placed, we will then broadcast the results, and I will read the votes aloud for the record.

Please note that once you've cast your vote, you may change it within the two-minute time frame. However, once the poll has closed, all votes will be considered final. So, unless anybody has any questions, we can pull up the voting pod, please.

Great. So, the poll is up, and if you can please cast your votes at this time.

Okay. Looks like all votes are in, so we can now broadcast the results, and I will read the votes aloud for the record. Dr. Moore voted yes. Dr. Wharton voted yes. Dr. Perlman voted yes. Dr. Sawyer voted yes. Dr. Nelson voted yes. Dr. Levy voted yes. Dr. Fuller voted yes. Dr. Hildreth voted yes. Dr. Cohn voted yes. Dr. Portnoy voted yes. Dr. Pergam voted yes. Dr. Lee voted yes. Dr. Offit voted yes. Dr. Monto voted yes. Dr. Kurilla abstained. Dr. Meissner voted yes. Dr. Rubin voted yes. Dr. Gans voted yes.

So, this concludes the vote. Out of 18 voting members, 17 voted yes, and we had one abstain. Thank you, Dr. Monto. I will turn it back to you for the voting explanation.

DR. ARNOLD MONTO: Thank you. Anybody who wants to further explain their vote, please raise your hand. Dr. Meissner?

DR. CODY MEISSNER: Thank you, Dr. Monto. I

voted yes as has been stated, but I wanted to make a point. I think that this is quite different than the MMR vaccine, for example. People compare it as it's a requirement to go to school to get the measles, mumps, rubella vaccine, and that I don't think is a fair comparison because we know that vaccine is safe. We have tested that vaccine for decades. We have a very good sense of what the adverse events are.

We do not have that with this particular messenger RNA vaccine. I'm saying there are some children that has been said in the 6- to 11-year-old group who are deserving of this and may very well derive benefit, but there are other children who may be at increased risk of myocarditis. Dr. Yang gave a very sophisticated mathematical model, but I just remind people that the rates of hospitalization in this age group of 6 to 11 is 0.1 per hundred thousand or less than 10 per million.

The rates of myocarditis in older age groups with a different vaccine from Israel, at least, were as high as a hundred to 150 cases per million. So, I

think we have to very carefully monitor the safety profile of this vaccine going forward if the ACIP does recommend it. And hopefully, it'll be for those children who have other risk factors.

DR. ARNOLD MONTO: Thank you, Dr. Meissner. Dr. Portnoy?

DR. JAY PORTNOY: Great. First of all, I wanted to thank you, Dr. Monto and the FDA, for holding such transparent and scientifically valid committee meetings like this. I think that having an open and transparent discussion like we did today instills confidence in the public so that they can see very clearly that we were very careful in our deliberations, and I think that the decision that we came to was exactly the right one. I'm very pleased with that.

I work at a children's hospital. Our hospital has been full for the last month or so with children who have been critically ill. Not all of them have COVID, but many of them do. We have a lot of them in the intensive care unit. I'm looking forward to being able to actually do something to prevent that. I'm

looking forward to seeing my patients tomorrow in the clinic because they've been terrified that their children are going to get COVID. Now I have some really good news for them that they can look forward to.

So, I want to thank the Committee for their deliberations. I think we made the right decision, and I look forward to telling my parents the good news.

DR. ARNOLD MONTO: Thank you, Dr. Portnoy. Dr. Cohn?

CAPT. AMANDA COHN: Thanks. So, COVID-19 now is a vaccine-preventable disease from my perspective, and COVID is also the eighth highest killer of kids in this age group over the past year. So, the use of this vaccine will prevent deaths. It will prevent ICU admission and will prevent significant long-term adverse outcomes in children. We will monitor myocarditis very carefully.

But I will also say that there have been no deaths from myocarditis and nearly all of those cases -- we were doing long-term outcomes -- have completely

recovered just weeks after the onset of their mild cases of myocarditis. So, I just really am so grateful that we had this discussion and that the Committee voted to approve this because I think that the benefits in this age group are really super important even if they are lower, per se, than older age groups.

I think this is an age group that deserves and should have the same opportunity to be vaccinated as every other age.

DR. ARNOLD MONTO: Thank you, Dr. Cohn. Dr. Levy?

DR. OFER LEVY: Thank you. I voted yes after some deliberation and hearing the latest phase of the discussion among the Committee members in FDA, which was helpful to me. Severe pediatric COVID is not nearly as common as an adult, but it does happen and it's not negligible. It does seem to me that we do need ongoing efforts by CDC and others to characterize the disease in children and to measure and define long COVID in children.

There's a lot of work to be done there. My

impression is not enough federal resources have been invested in those directions, and I would encourage the system to continue to do that. I think this vaccine will likely be effective in reducing pediatric COVID in this age group and may also help reduce transmission.

On the safety end, I'm encouraged by the lower dose. The dose-finding, finding a dose that's immunogenic and had not too much in terms of reactogenicity.

Then in terms of the myocarditis, it will be important to keep an eye on that as Dr. Cohn alluded to given the surveillance and yet, a priority that seems the 5- to 11-year age group may be less susceptible to that. CDC, if FDA decides to proceed with this, CDC will take it up and will consider the data with an independent eye in terms of whether they need to direct towards how this would be deployed and how it would be used.

And I think that the surveillance systems are going to be critical here, and I'm hoping that this starts off as a campaign, if it moves forward, that

starts with choice and parents and their care providers partnering in those decisions. Thank you.

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

DR. ERIC RUBIN: (Audio skip) still get FDA approved and it goes to ACIP, if they produce a recommendation that says that there will be discretion in how it's used as opposed to a mandate, which I think we would all be concerned about at this point, we are going to get plenty of experience with this, and the good pharmacovigilance plans, I think, are going to be very useful.

We will know how safe this is. I agree with Dr. Cohn. You want to save because you can save. I do think that it will be useful to have a lot more information, though, to determine how best to deploy the vaccine. So, I think that we ended up sort of in between. We decided to go for it with a lot of heavy conscious, but I'm hoping that this is the start of learning more about it.

DR. ARNOLD MONTO: Dr. Wharton?

DR. MELINDA WHARTON: So, I think this is a

valuable tool for prevention of COVID. I know that I've been very worried hearing about pediatric hospitals and pediatric intensive care units being full over the previous several months during the Delta surge in so many communities. So, having this vaccine available to prevent COVID in 5- to 11-year-olds seems to me to be a really positive step.

Of course, we will learn more about safety as things go forward, but I think, based on the lower background rate of myocarditis in this age group, the lower dose being used, and the evidence that risk is lower in the younger adolescents than the older adolescents, together, I think that I am not as concerned about myocarditis in this age group as I am in the older kids. So, I think it's a good move forward for COVID prevention and for protecting our kids.

DR. ARNOLD MONTO: Thank you, Dr. Wharton. Dr. Pergam?

DR. STEVEN PERGAM: So, I really hope that as we think about this, we focus similarly the way we did

on adults that mandates were not immediate after the vaccine was approved, and we see sort of a delay in that sort of approach because I think there is -- the safety concerns are things that have been brought up by Committee members, and there is some issues that folks have, but we want to make sure that we're doing right by children by giving them the opportunity to get vaccinated as well.

So, I think that's going to be an important piece as we move forward. You've heard that from Committee members that there is some concern about school mandates and such at the moment. So, I think it's important to keep that in mind, at least in the short term. I also think this sort of begs another question that I think we haven't talked about enough is that we don't do enough in early phases of vaccine trials to include children.

Obviously, when they're pediatric vaccines, that's different, but I think we need to rethink our strategies and how we do this because having this data a few months back would've been very valuable as we

think about this, and I think, yes, I'd love to see the FDA rethink how they want to advise vaccine companies about doing this kind of research because having this in the earlier phase, and I think my pediatric colleagues would agree with this, would be very advantageous.

DR. ARNOLD MONTO: Thank you. Dr. Hildreth?

DR. JAMES HILDRETH: Thank you, Dr. Monto. I voted yes primarily because I want to make sure that the children who really need this vaccine, primarily black and brown children in our country, get the vaccine, but, to be honest, the best way to protect the health of some kids would be to do nothing at all because they're going to be just fine. There are lots and lots of children who, for this vaccine, would be the difference between health and even life.

So, my vote was primarily to make sure that those who really need it can get it. I hope that the ACIP will prioritize the vaccine in some ways to make sure that that actually happens, but that's why I voted yes, is to make sure that those who really need it can

get it. Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Moore, final comment.

DR. PATRICK MOORE: Thank you, Arnold. One thing that I hope is that this is not a last step, but just very, very tiny first step and that the -- I really hope that Pfizer and that the national research agencies -- NIH, FDA, CDC -- do put serious effort into seeing how we can improve the use of this vaccine, particularly in these younger age groups. Or the J&J vaccine, for example, how can that be improved so that the public has more confidence that we are authorizing a vaccine that is as possibly safe and protective as we can get?

I think it's too easy for these institutions to simply say, well, we've gotten over the hurdle of it. It's been accepted in this age group or this risk group; let's move on to the next thing. I was a little disappointed that the clinical trials for children didn't start until June 1st of this year, whereas this time last year, we were evaluating the clinical trials

for 18-year-olds and above for the Pfizer vaccine, and then quickly thereafter for the Moderna vaccine.

So, I just hope that we can make a little bit better progress on trying to find out how to optimize our tools to fight against this virus.

DR. ARNOLD MONTO: Thank you very much, Dr. Moore. Just to continue some of your thoughts, this could be not the last step but the first step in understanding the role of these vaccines in the pediatric age group. We've identified a lower dose, which we expect is going to decrease the frequency of the rare side effect of myocarditis. We may want to look at that dose in other age groups where myocarditis is more frequent.

We have approved or recommended approval for a three-week interval. That's something that we also need to look at more closely, but this is what we have to do now because we are in an emergency. I thank the Committee for a very long and very deliberate and very complete review of all of the elements that have gone into our recommending approval of this vaccine for an

important age group of children. So, over to you, Prabha, to close the meeting.

MEETING ADJOURNMENT

DR. PRABHAKARA ATREYA: Thank you, Dr. Monto. Actually, I will invite Dr. Marks to make the closing remarks before I formally adjourn the meeting.

DR. PETER MARKS: Thank you very much to the entire Committee for what were very, very thoughtful deliberations today. I think it obviously is a challenging thing, and I think it all shows how caring the entire Committee is about our children. I think everyone here is trying to weigh -- do their best to weigh the benefits and risks here.

Just to reassure the Committee, because we are taking an emergency use authorization rather than approval, in general -- although it's possible that mandates could be put in place, I suppose. In general, people have not done mandates with emergency use authorizations, and there are certain governors who

have already announced that they would not do a mandate until there was an approval as opposed to an emergency use authorization.

So, I really appreciate very much the concern here. The other thing I would just like to just stress is that the safety monitoring of this vaccine will continue. It has actually been quite intense with a small army of individuals who are very committed to this, and they will continue this.

I do view this as one of our greatest responsibilities to ensure that, as this vaccine is deployed and as it continues to be deployed in both adults, adolescents, and children, that we are very actively looking for any safety signals and that we take rapid action, and we do so in conjunction with our colleagues at CDC.

So, thank you all again for what was a very long day. We greatly appreciate your input and wish you a very good rest of day.

DR. PRABHAKARA ATREYA: Thank you, Dr. Marks. This is now to formally adjourn the meeting. The

meeting is adjourned at 4:35 p.m. Eastern Time. Thank you so much.

[MEETING ADJOURNED]