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Center for Biologics Evaluation and Research (CBER)
166th Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting

OPEN SESSION

Web-Conference
Silver Spring, Maryland 20993

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

ATTENDEES

COMMITTEE MEMBERS	
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CAPT Amanda Cohn, M.D.	National Center for Immunizations and Respiratory Diseases Centers for Disease Control and Prevention
Hayley Gans, M.D.	Stanford University Medical Center
Michael Kurilla, M.D., Ph.D.	National Institutes of Health
H. Cody Meissner, M.D.	Tufts University School of Medicine
Paul Offit, M.D.	The Children's Hospital of Philadelphia
Steven A. Pergam, M.D., M.P.H., FIDSA	Seattle Cancer Care Alliance
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A. Oveta Fuller, Ph.D.	University of Michigan
James Hildreth, Sr., Ph.D., M.D.	Meharry Medical College
David Kim, M.D., M.A.	U.S. Department of Health and Human Services
Ofer Levy, M.D., Ph.D.	Massachusetts Institute of Technology
Pamela McInnes, D.D.S., M.Sc.	National Institutes of Health
Arnold Monto, M.D.	University of Michigan
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

Eric Rubin, M.D., Ph.D.	Brigham and Women's Hospital
Mark Sawyer, M.D., F.A.A.P.	Rady Children's Hospital San Diego
Melinda Wharton, M.D, M.P.H.	Centers for Disease Control and Prevention
SPEAKERS AND GUEST SPEAKERS	
Hannah Kirking, M.D.	Centers for Disease Control and Prevention
Arthur Phyllis, M.B.A	Biotechnological Innovation Organization
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OPENING REMARKS: CALL TO ORDER, INTRO OF COMMITTEE

MR. MICHAEL KAWCZYNSKI: All right. Good morning and welcome to the 166th meeting of the Vaccines and Related Biological Products Advisory Committee meeting. I'm Mike Kawczynski, a project manager with FDA, and I'll be today's meeting facilitator.

This is a live virtual public meeting that is being broadcast in its entirety through C-SPAN, Yorkcast, Facebook Live, YouTube, Twitter, and many other avenues. Today's event is also being recorded and will be posted on FDA's VRBPAC webpage along with all relevant meeting materials.

Throughout today's meeting, I will be reminding our speakers and presenters and Committee members as to when they are close to their allotted time and assisting them when needed. Just as a reminder to everyone that once called upon to please manage your mute and activate your webcams. If we encounter any technical issues throughout the day, we

may have to take an unscheduled break.

At this time though, I'd like to get the meeting started, and I'd like to introduce you to Dr. Arnold Monto, the acting chair, who will now provide opening remarks. Dr. Monto, you're ready? Take it away.

DR. ARNOLD MONTO: Thank you, Mike. I'd like to add my welcome to the 166th meeting of the Vaccines and Related Biological Products Advisory Committee of the Center for Biologics Evaluation and Research. It is my pleasure to open the meeting and to remind you of the one topic that we have for the meeting. We will meet in open virtual session to discuss, in general, data needed to support authorization and/or licensure of COVID-19 vaccines for use in pediatric populations.

So I'd like now to hand over to our designated federal officer, Prabha Atreya, who will give the administrative announcements, the roll call, and introduce the Committee. Prabha.

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

DR. PRABHAKARA ATREYA: 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 the DFO -- for today's 166th Vaccines and Related Biological Products Advisory Committee. On behalf of the FDA, the Center for Biologics Evaluation and Research, and the Committee, I would like to welcome everyone to today's virtual meeting. Like Dr. Monto mentioned, the topic for today's meeting is to discuss, in general, data needed to support authorization and/or licensure of COVID-19 vaccines for use in pediatric populations. Today's meeting and the topic were announced in the Federal Register Notice that was published on May 21, 2021.

I would like to introduce and acknowledge the excellent contributions of the staff in my division and the great team I have in preparing for this meeting. Ms. Kathleen Hayes is my backup DFO and co-DFO,

providing excellent support in all aspects of preparing for and conducting this meeting. Other staff who contributed significantly are Ms. Monique Hill, Dr. Jeannette Devine, Ms. Christina Vert, who provided excellent support. I would also like to express our sincere appreciation to Mr. Mike Kawczynski in facilitating the meeting for today. And also our kudos to many of the FDA staff working behind the scenes really hard to make sure that today's virtual meeting will also be a successful one like the previous four VRBPAC meetings on the COVID topic.

Please direct any press or media questions for today's meeting to FDA's Office of Media Affairs at FDAOMA -- one word -- @fed.hss.gov. The transcriptionist for today's meeting is Ms. Linda Giles.

We will begin today's meeting by taking a formal role call for the Committee members and temporary voting members. When it is your turn, please turn on your video camera, unmute your phone, and then state your first and last name. And then, when

finished, you can turn your camera off so we can proceed to the next person. Please see the member roster slide in which we will begin with the chair. Dr. Arnold Monto, can we please start with you? Thank you. Mike, can we see that slide, the roster slide? The next one, please.

DR. ARNOLD MONTO: I'm Arnold Monto. I'm professor of epidemiology at the University of Michigan School of Public Health, and my area of expertise is infectious disease, epidemiology, and disease prevention. Prabha.

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

CAPT. AMANDA COHN: Good morning, everyone. I'm Dr. Amanda Cohn, the chief medical officer at the National Center for Immunizations and Respiratory Diseases with expertise in pediatrics and vaccines and epidemiology.

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

DR. ARCHANA CHATTERJEE: Good morning,

everyone. I'm Archie Chatterjee, Dean of Chicago Medical School and Vice President for Medical Affairs at Rosalind Franklin University of Medicine and Science. I'm a pediatric infectious diseases specialist by background and training with a focus on vaccinology.

DR. PRABHAKARA ATREYA: Thank you. Dr. Cody Meissner. We can't hear you, Dr. Meissner. You need to turn on your speaker.

DR. CODY MEISSNER: Good morning. My name is Cody Meissner. I'm a professor of pediatrics at Tufts University School of Medicine and Tufts Children's Hospital. My area of interest is infectious disease, and I've had more than 35 years of experience with pediatric immunizations. Thank you.

DR. PRABHAKARA ATREYA: Thank you. Next slide, please. Dr. Gans.

DR. HAYLEY GANS: Good morning. I am Dr. Hayley Gans. I'm a professor of pediatrics and pediatric infectious disease at Stanford University, and my research focus is on the immune response to

vaccines in multiple different populations, including children and immunocompromised adults.

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

DR. MICHAEL KURILLA: Morning. Michael Kurilla. I'm the director of the Division of Clinical Innovation at the National Center for Advancing Translational Sciences within NIH. I'm a pathologist by training and a background in infectious disease product development including drugs, vaccines, and diagnostics.

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

DR. PAUL OFFIT: Yeah. Good morning. I'm Paul Offit. I'm in the Division of Pediatric Infectious Disease at the Children's Hospital of Philadelphia and a professor of pediatrics at the University of Pennsylvania School of Medicine. My expertise is in the area of vaccines and vaccine safety. Thank you.

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

DR. PAULA ANNUNZIATO: Good morning. I'm Paula Annunziato. I lead vaccines clinical development at Merck, and I'm here today as the non-voting industry representative.

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

DR. STEVEN PERGAM: Hello, everyone. I'm Steve Pergam. I'm an infectious disease physician in Seattle, Washington, and I work at the Fred Hutchinson Cancer Research Center. My area of focus is in the immunocompromised population.

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

DR. OVETA FULLER: Good morning. I'm Oveta Fuller. I'm an associate professor of microbiology and immunology at the University of Michigan Medical School. My expertise is virology and community engagement for disease prevention.

DR. PRABHAKARA ATREYA: Thank you. Dr. Kim. David Kim.

DR. DAVID KIM: Good morning. This is David

Kim. I'm the director of the Division of Vaccines in the Office of Infectious Disease and HIV/AIDS Policy, which is under the Office of the Assistant Secretary for Health. My interest is in vaccines.

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

DR. ERIC RUBIN: Hi. I'm Eric Rubin. I'm at the Harvard TH Chan School of Public Health at the Brigham and Women's Hospital and editor-in-chief of the *New England Journal of Medicine* and an infectious disease physician.

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

DR. JAMES HILDRETH: Good morning. I'm James Hildreth. I'm the president at Meharry Medical College and professor of internal medicine. My expertise is in immunology and viral pathogenesis. Thank you.

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

DR. JAY PORTNOY: Good morning. I'm Dr. Jay Portnoy. I'm a professor of pediatrics at the University of Missouri, Kansas City School of Medicine.

And I'm also an allergist/immunologist at Children's Mercy Hospital in Kansas City.

DR. PRABHAKARA ATREYA: Okay. Thank you. Dr. Dodd. We can't hear you, Dr. Dodd. You need to turn on your speakers.

DR. LORI DODD: There we go. How's that?

DR. PRABHAKARA ATREYA: Yes, that's better. Thank you.

DR. LORI DODD: Yeah. Okay. Thank you. I'm Lori Dodd. I'm a biostatistician. I'm a member of the Biostatistics Research Branch at NIAID as well as the chief of the Clinical Trials Research Section. My expertise is in clinical trials and infectious diseases. Thank you.

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

DR. MARK SAWYER: Good morning. My name is Mark Sawyer.

DR. PRABHAKARA ATREYA: We can't hear you. Now we can.

MR. MICHAEL KAWCZYNSKI: We can hear you.

Continue.

DR. MARK SAWYER: Good morning. My name is Mark Sawyer. I am a professor of pediatrics and pediatric infectious diseases at University of California San Diego and Rady Children's Hospital San Diego.

DR. PRABHAKARA ATREYA: Thank you. Dr. Melinda Wharton.

DR. MELINDA WHARTON: I'm Melinda Wharton. I'm director of the Immunization Services Division at the Centers for Disease Control and Prevention. I'm an adult infectious disease physician by training, and my expertise is in vaccines and vaccine programs.

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

DR. MICHAEL NELSON: Hi. I'm Mike Nelson. I'm a professor of medicine and chief of the Asthma, Allergy, and Immunology Division at the University of Virginia, as well as president of the American Board of Allergy and Immunology. I recently retired from Army Medicine at Walter Reed. My interests are vaccine

immune responses and adverse events. Thank you.

DR. PRABHAKARA ATREYA: Thank you, Dr. Nelson. Dr. Levy.

DR. OFER LEVY: Hello. Good morning. My name is Ofer Levy, and I'm director of the Precision Vaccines Program at Boston Children's Hospital and professor of pediatrics at Harvard Medical School.

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

DR. PAMELA MCINNES: Good morning. I'm Pamela McInnes, retired now from the National Center for Advancing Translational Sciences at the National Institutes of Health and had a long-standing interest and work record in vaccines and other biologicals. Thank you.

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

DR. STANLEY PERLMAN: Oh. Good morning. Can you hear me now?

DR. PRABHAKARA ATREYA: Yes. Go ahead, please.

DR. STANLEY PERLMAN: Okay. I'm just trying to -- okay. Yeah, I'm Dr. Stanley Perlman. I'm a professor of microbiology and immunology and pediatrics and a pediatric infectious disease physician by training. I'm at the University of Iowa, and my expertise is in coronavirus immunology, virology, and pathogenesis.

DR. PRABHAKARA ATREYA: Thank you. Now I would like to introduce our FDA staff. First, I would like to introduce Dr. Marion Gruber, Director, Office of Vaccines, who will say a few welcome remarks. Dr. Gruber, go ahead, please.

DR. MARION GRUBER: Yeah. Good morning. Can you hear me?

DR. PRABHAKARA ATREYA: Yes. Yes.

DR. MARION GRUBER: Okay. Great. Yeah, my name is Marion Gruber, and I'm the director of the Office of Vaccines Research and Review at CBER at FDA. On behalf of my colleagues in OVRR and the Center, I would like to welcome the VRBPAC members to today's meeting. This is the fifth VRBPAC meeting convened

over the last seven to eight months to discuss COVID-19 vaccines, but today's topic is of particular importance to our stakeholders, the American public and parents, as we ask you to discuss considerations and data to support licensure or emergency use authorization of COVID-19 vaccines for use in pediatric populations 6 months to less than 18 years of age.

Your perspectives and opinions regarding approaches to evaluating COVID-19 vaccine effectiveness and, in particular, safety to support the use in pediatric populations as described in our briefing document -- and this will be discussed further this morning -- will help the FDA to advise COVID-19 vaccine manufacturers to ensure that pediatric trials will be adequate to support vaccine licensure and, as needed, emergency use authorization in these groups. Severe COVID-19, resulting in hospitalization and death, does occur in infants and children. However, the COVID-19 disease burden is generally lower in younger pediatric age groups compared with adolescents and adults. In recent times, we also have become aware of rare adverse

events after the administration of some of the COVID vaccines, the most recent reports of myocarditis observed in adolescents and young adults following the administration of some of these vaccines.

Therefore, risk-benefit considerations to determine whether to issue an emergency use authorization for use of COVID-19 vaccine to healthy pediatric individuals will need to account for this inflammation, and the risk-benefit consideration will likely be different, not only compared to those for adults. But also they may be different for younger versus older pediatric age groups. To facilitate your deliberations, we have formulated three non-voting discussion items, but we welcome your insight on other aspects of this complex topic as we intend to take the different perspectives that we will be hearing and expressed today into consideration in refining our approach to evaluating COVID-19 vaccine safety and effectiveness in pediatric populations. Thank you, and I look forward to the Committee's discussions.

DR. PRABHAKARA ATREYA: Thank you, Dr.

Gruber. I would also like to acknowledge the presence of Dr. Celia Witten, the Deputy Director of CBER, and Dr. Philip Krause, Deputy Director of the Office of Vaccines at this meeting. Dr. Peter Marks, our Center director, will join us later in the day to make his remarks addressing the Committee.

Now, I will proceed with the reading of the conflict of interest statement for the public record. Thank you. The Food and Drug Administration is convening virtually today, June 10th, 2021, for the 166th meeting of the Vaccines and Related Biological Products Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. Dr. Arnold Monto is serving as the acting voting chair for today's meeting.

Today, on June 10th, 2021, the Committee will meet in open session to discuss data to support authorization and/or licensure of COVID-19 vaccines for use in pediatric populations. This topic is determined to be of particular matter involving specific parties. With the exception of the industry representative

members, all standing and temporary voting members of the VRBPAC are appointed as special government employees, SGEs, or regular government employees, RGEs, from other agencies and are subjected to federal conflicts of interest laws and regulations.

The following information on the status of this Committee's compliance with federal ethics and conflict of interest laws including, but not limited to, 18 United States Code Section 208 is being provided to participants in today's meeting and to the public. Related to the discussions at this meeting, all members, RGEs and SGEs, and 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 purposes 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 assignments, patents and royalties, and 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 the federal ethics and conflict of interest laws. Under 18 U.S. Code Section 208, Congress has authorized the FDA to grant waivers to special government employees and regular government employees who have financial conflicts of interest when it is determined that the Agency's need for the special government employee's services outweigh the potential for the conflict of interest created by the financial interest involved or when the interest of a regular government employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Based on today's agenda and all financial conflict of interest 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

conflict in serving as a temporary voting member as you have heard before: Dr. Lori Dodd, Dr. Oveta Fuller, Dr. James Hildreth, Capt. David Kim, Dr. Ofer Levy, Dr. Pamela McInnes, Dr. Arnold Monto, Dr. Michael Nelson, Dr. Stanley Perlman, Dr. Jay Portnoy, Dr. Eric Rubin, Dr. Mark Sawyer, and Dr. Melinda Wharton. Among these consultants, Dr. James Hildreth, a special government employee, has been issued a waiver for his participation in today's meeting. The waiver was posted on the FDA's website for public disclosure.

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

Dr. Jay Portnoy is serving as the acting

consumer rep for this Committee. Consumer representatives are appointed as special government employees and are hence screened and cleared prior to their participation in the meeting. They are voting members of the Committee.

Disclosures 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 interests they may have with any affected firms, its products, or if known, its direct competitors. We would like to remind standing and temporary members that if the discussions involve any of the products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to inform the DFO and exclude themselves from such involvement, and their exclusion will be noted for the record.

This concludes the reading of the conflict of interest statement for the public record. At this

time, I would like to hand over the meeting to our Chair, Dr. Arnold Monto. Dr. Monto, I kick the meeting back to you. Thank you. Dr. Monto?

MR. MICHAEL KAWCZYNSKI: I believe Dr. Monto -- I'm not quite sure if Dr. Monto's audio is connected at the moment, so, while we're waiting for Dr. Monto's audio to come back in, Prabha, I believe, can you announce the first speaker, Dr. -- are we allowed to --

DR. PRABHAKARA ATREYA: Yes.

MR. MICHAEL KAWCZYNSKI: -- or should we wait? Okay. Do you want to go ahead and introduce the first speaker? And then we'll help Dr. Monto when he gets back.

FDA INTRODUCTION

DR. PRABHAKARA ATREYA: Okay. On behalf of Dr. Monto, I'm going to introduce the first speaker of the FDA's presentation, Dr. Ramachandra Naik, Ph.D. He's a biologist in the Division of Vaccines and Related Product Applications, Office of Vaccines. Dr.

Naik, go ahead, please.

DR. RAMACHANDRA NAIK: Good morning, everyone. I'm Ram Naik from the Division of Vaccines and Related Products Applications in the Office of Vaccines Research and Review at CBER/FDA. I'm going to provide a brief introduction for today's Advisory Committee meeting regarding licensure and emergency use authorization of vaccines to prevent COVID-19 for use in pediatric populations.

As you all know, the SARS-CoV-2 pandemic still continues in the U.S. and worldwide. The ongoing COVID-19 pandemic has affected individuals of all ages in the U.S. Although incidence and severity of disease are generally lower in pediatric populations compared with adults, cases of severe COVID-19, resulting in hospitalization and death, have occurred in pediatric populations. CDC speakers will provide more specific details regarding the epidemiology of COVID-19 in the pediatric population.

COVID-19 vaccination is an important public health measure to control SARS-CoV-2 in pediatric and

other age groups. Now, there is an intense interest in pediatric COVID-19 vaccines.

Regarding the requirements of BLA, a single set of basic regulatory requirements applies to all vaccines, regardless of the technology used to produce them. Section 351 of the Public Health Service Act, states that "A BLA can be approved based on a demonstration that the biological product... is safe, pure, and potent, and the facility in which the biological product is manufactured meets standards designed to assure that the biological product continues to be safe, pure, and potent."

To facilitate the manufacturing, clinical development, and licensure of COVID-19 vaccines, FDA published a Guidance for Industry in June 2020, which provides an overview of key considerations to satisfy regulatory requirements set forth in the IND regulations and licensing regulations for CMC and non-clinical and clinical data through development and licensure and for post-licensure safety evaluation of COVID-19 vaccine. The guidance notes that the efficacy

of COVID-19 vaccines should be demonstrated in adequate and well-controlled clinical trials that directly evaluate the ability of the vaccine to protect humans from SARS-CoV-2 infection and/or disease. Additionally, the guidance notes that the safety evaluations, including the size of the database required to support licensure, should be no different than for other preventive vaccines for infectious diseases.

Based on the declaration by the Secretary of the U.S. Department of Health and Human Service that the COVID-19 pandemic constitutes a public health emergency, FDA may issue an EUA for a medical product after determining that certain statutory requirements are met. As an EUA of a COVID-19 vaccine allows for the rapid and widespread deployment for administration to millions of individuals, including healthy people, issuance of an EUA requires a determination that the known and potential benefits of the investigational product outweigh its known and potential risks based on the data from at least one well-controlled Phase 3

clinical trial demonstrating vaccine safety and efficacy in a clear and compelling manner. Issuance of an EUA for an investigational COVID-19 vaccine would require adequate manufacturing information to ensure the products for quality and consistency.

FDA published "Guidance for Industry: for EUA for Vaccines to Prevent COVID-19" originally issued in October 2020 and revised later. The guidance describes the FDA's current recommendations regarding the need for manufacturing non-clinical and clinical data and information to support the issuance of an EUA for an investigational vaccine to prevent COVID-19. The guidance also includes the advice the FDA has been providing to the potential vaccine developers.

Previously, as Dr. Gruber said, a total of four VRBPAC meetings occurred to discuss development, authorization, and/or licensure of COVID-19 vaccines. The VRBPAC met on October 22, 2020, to discuss, in general, the development, authorization, and/or licensure of COVID-19 vaccines. No specific application was discussed at this meeting. On December

10, 2020, the VRBPAC met to discuss the EUA request for the Pfizer-BioNTech COVID-19 vaccine. On December 17, 2020, the VRBPAC met to discuss the EUA request for the Moderna COVID-19 vaccine. And on February 26, 2021, the VRBPAC met to discuss the EUA request for the Janssen COVID-19 vaccine.

Currently, there are three COVID-19 vaccines available for use under the EUA: Moderna and Janssen COVID-19 vaccines are authorized for use in adults 18 years of age and older. Pfizer-BioNTech COVID-19 vaccine was originally authorized for use in individuals 16 years of age and older. However, last month, FDA granted an extension of emergency use of this vaccine in adolescents 12 through 15 years of age. Moderna's EUA amendment for adolescents was submitted for FDA review on June 9th, 2021. So currently, there are no approved or authorized COVID-19 vaccines for pediatric populations less than 12 years of age.

This is the overview of today's agenda. After this introduction, CDC's Dr. Hannah Kirking is going to talk on the epidemiology of COVID-19 in pediatric

populations, followed by CDC's Dr. Shannon Stokley who speaks on operational aspects. Post authorization surveillance activities will be presented by FDA's Dr. Steve Anderson and CDC's Dr. Tom Shimabukuro, followed by the break.

After the break, FDA's Dr. Doran Fink is going to present on considerations on data to support licensure and emergency use authorization of COVID-19 vaccines for use in pediatric populations, followed by an additional question and answer session. Phyllis Arthur of Biotechnology Innovation Organization is going to present "Industry Perspective: Considerations for COVID-19 Vaccine Pediatric Trials," followed by a lunch break. After the lunch break, there will be an open public hearing and, at the end, the Committee discussion and comments.

There are three items for discussion today. No voting on these items. The first item is: provided there is sufficient evidence of effectiveness to support the benefit of a COVID-19 preventive vaccine for pediatric age groups, for example, 6 to less than

12 years, 2 to less than 6 years, and 6 months to less than 2 years, please discuss the safety data, including database size and duration of follow-up, that would support Emergency Use Authorization and licensure.

Item 2 is: provided there is sufficient evidence of effectiveness to support the benefit of a COVID-19 preventive vaccine for adolescents 12 to less than 18 years of age, please discuss the safety data, including database size and duration of follow-up, that would support licensure. Item 3 is: please discuss studies following licensure and/or issuance of an EUA to further evaluate the safety and effectiveness of COVID-19 vaccines in different pediatric age groups. Thank you.

MR. MICHAEL KAWCZYNSKI: All right. Arnold, let me make sure you're unmuted. Dr. Monto, are you back?

DR. ARNOLD MONTO: Okay. This is Arnold Monto again. I've got audio but no video, so let's, first of all, thank Dr. Naik for your introduction which has covered some of the key points that we're going to be

discussing later on. Let's move on now to Dr. Hannah Kirking, who is from the Medical Epidemiology, Division of Viral Diseases, Respiratory Virus Branch.

MR. MICHAEL KAWCZYNSKI: Dr. Monto, we still have time for the Q and A.

DR. ARNOLD MONTO: Oh, we have a Q and A. Okay. Excuse me.

MR. MICHAEL KAWCZYNSKI: It's all right, sir.

DR. ARNOLD MONTO: All these technology issues. We do have time. We've got about more than five minutes for Q and A. Questions for Dr. Naik, especially about the discussion questions we're going to be getting into later on. Dr. Meissner, I see you're up there.

DR. CODY MEISSNER: Yes, sir. Thank you, Dr. Naik. I appreciate your presentation this morning. I would like to ask you a specific question, and I'm not sure who it should be addressed to. But perhaps you can answer.

I'm thinking back over three of the recently FDA-licensed vaccines for children, and I think of the

dengue vaccine, Dengvaxia. I think of the human papillomavirus vaccine. I think of the rotavirus vaccine. Can you remind us how many subjects were enrolled in those trials before approval or licensure was granted because I think it was tens of thousands of participants? But perhaps you can remind us of the actual numbers.

DR. RAMACHANDRA NAIK: I would invite my FDA colleagues to answer this question. I'm not aware of that specific information.

DR. ARNOLD MONTO: Dr. Fink.

DR. DORAN FINK: Hi. Dr. Meissner, I can try to answer your question. So, for the dengue vaccine, you're talking about Dengvaxia, which was approved in 2019. This was a vaccine that was approved for use in ages 9 through 16 years, so entirely a pediatric population with no adult safety data available at that time. It was approved based upon a clinical endpoint efficacy study that was adequately powered to formally test via statistical hypotheses the efficacy of the vaccine against dengue, and so by necessity of the

efficacy endpoint trial design, that safety database was in the upwards of 10,000 pediatric recipients in that age group of 9 to 16 years.

In terms of the Gardasil vaccine, the safety database for pediatric age groups, which was initially 16 to less than 18 years of age -- those were included amongst the total initial age group of 16 to 26 years of age for which the vaccine was approved. That was less; that was in the thousands. (Inaudible) accompanying adult safety data along with that approval initially for use in older adolescents. We then had studies in several thousand pediatric-aged individuals who are younger adolescents and some younger children, so 9 to 15 years of age.

And then for the rotavirus vaccine, these safety databases were in the high tens of thousands, so 60-, 70,000. That was driven by clinical endpoint efficacy study considerations again and also the desire to investigate a specific adverse reaction into susception, which, based on experience with previous vaccines, was suspected to occur uncommonly.

DR. CODY MEISSNER: Thank you.

DR. ARNOLD MONTO: Any other questions before we move on? Oh, I see Dr. Rubin's got his hand raised. Dr. Rubin.

DR. ERIC RUBIN: Yeah, just to follow up on with a comment more than a question. As I understand it, those vaccines for which we had -- that Dr. Fink was discussing that had tens of thousands of children involved had no adult safety data. So it's a little -- slightly different case, is that right?

DR. DORAN FINK: Yes. Yes, that's correct. So, as I mentioned for both the dengue vaccine and for the rotavirus vaccines, we had no experience in adults prior to approval of those vaccines for use in the respective pediatric populations. With HPV vaccines where the safety database was less compared to the rotavirus and dengue vaccines, we did have experience in adults.

DR. ARNOLD MONTO: Thank you. We're sort of -- Dr. Fink, before you go, I just want to -- we're getting a little ahead of the game because our

discussion, which we have a lot of time for, is this afternoon. But I wanted to raise another issue to think about as we go through, and that is that, because of the experience with adults, when we have our discussion, we are to focus on safety issues and not on efficacy issues. Is that correct?

DR. DORAN FINK: So I will cover this during my presentation. We are asking the Committee to focus their discussion on safety issues. We have a very well-established regulatory precedent for demonstrating effectiveness in pediatric populations, including in the situation where clinical endpoint efficacy for the vaccine has previously been demonstrated in adults. So I will get into those details during my presentation. But, yes, we are asking the Committee to focus their discussion on safety issues.

DR. ARNOLD MONTO: Right. I just wanted to bring that up because we, again, are getting ahead of the game, so I just want to keep everything in mind so that we remember all this as we go through the next presentations. Thank you, Dr. Fink. And now, finally,

I will call on Dr. Kirking -- Dr. Hannah Kirking from the Respiratory Virus Branch at CDC who will tell us about the epidemiology of COVID-19 in pediatric populations. Dr. Kirking, thank you.

CDC: EPIDEMIOLOGY OF COVID-19 IN THE PEDIATRIC POPULATIONS

DR. HANNAH KIRKING: Okay. Good morning, everyone. Thank you for having me, and I appreciate the opportunity to talk a little bit more about the epi component of the discussion.

I'd like to start with a brief overview of the current status of the SARS-CoV-2 pandemic globally and within the United States. As of June 1st, there have been over 170 million confirmed cases of SARS-CoV-2 with over 3.5 million deaths. The burden of the disease has been highest in the WHO regions of the Americas and Europe. Incidence globally of SARS-CoV-2 reached its highest peak in mid-April, driven largely by cases in Southeast Asia. This occurred after a

previous peak in January of 2021 that was driven by cases in the Americas and in Europe. Globally, the incidence of cases has increased and decreased over time, and the trends have been driven by different geographic regions.

This slide shows the daily and moving seven-day average incidents of SARS-CoV-2 cases within the United States. As of June 4th, there were over 33 million total cases reported. The current seven-day average of 14,349 daily new cases continues a downward trajectory with a 35.2 percent decrease compared to the week prior.

Similarly, this graph shows SARS-CoV-2 deaths in the United States over time. Almost 600,000 deaths have been attributed to SARS-CoV-2. The seven-day moving average count on June 4th was down 21.6 percent compared to the week prior. For the most part, trends in deaths continue to follow the trends in case counts.

Now, let's transition and talk specifically about the epidemiology of COVID-19 in children and adolescents. I thought we would first start with a

review of what is already published as there are numerous published studies and reviews. Early reports that relate to the epidemiology of SARS-CoV-2, in children specifically, largely utilize convenience and/or observational data. This was largely an opportunistic use of data that was available while better systems and/or studies were being developed and/or starting to enroll participants.

The other thing to note is that analyses of "children" often include participants less than 18 years of age all grouped together. In summary, the published literature on infection and transmission of SARS-CoV-2 and children remains largely mixed. Some studies suggest that children are infected less; others show that infection rates are similar to those seen in adults. Some studies show that children transmit virus less, and others show that transmission is similar for children as it is in adults.

I want to review a couple of important epidemiologic principles before I transition to highlighting some of the important data. First and

foremost, young children are not physiologically or socially equivalent to older children, adolescents, or adults. I realize everyone probably is well aware of this, but it's a reminder that age should be disaggregated whenever possible, for example, into finer age bands of less than 5 years, 6 to 11 years, or 12 to 17 years as an example.

Secondly, we have to be aware of biases on interpreting data related to COVID-19 in children. Exposures and behaviors both impact the observed infection rates that we see, not only biologic differences. Incidence and transmission estimates should be unbiased by care-seeking behavior. So, in short, if you do not look for infected children outside of clinical studies, you're probably going to miss them.

And lastly, universal testing is important when trying to understand the epidemiology of COVID-19 in children. Testing should be done independent of presence or absence of symptoms when trying to better understand rates of infection and transmission risks.

So the epidemiology of COVID-19 in children definitely differs from that in adults. This is due to many factors that ultimately lead to a child becoming infected or not infected. Each is important for understanding the transmission patterns, and this is kind of breakdown of the important epidemiologic factors for us to consider and that we do have increasing data to inform our understanding.

To start with, in general, children are susceptible to SARS-CoV-2 infection. From various studies, when testing systematically in children exposed to SARS-CoV-2, children are as likely to have infections detected as adults. However, one caveat to consider is that the risk of exposure for children relative to adults has changed dramatically over the course of the pandemic. For example, at the start of the pandemic, full societal shutdowns likely benefitted children more than adults, meaning it likely reduced exposures for children more than it did for adults. This pattern that we see as kids relative to adult has likely dramatically changed when schools reopened and

when society has reopened more broadly, which does change the risk for children.

The next factor considered is the risk for transmission. Children or adolescents can transmit SARS-CoV-2, and I'll review some data specifically on this topic. We now have studies with strong methods that account for differences and exposures and include universal testing. Within these studies, we are seeing that children are transmitting SARS-CoV-2.

And then, finally, there's clinical factors and outcomes to consider. Children and adolescents are less likely to seek testing for SARS-CoV-2 and are less likely to require medical care. This is due to the fact that the risk for systematic and severe illness is lower in children and in adolescents relative to most adult age groups.

Now, I want to review some important and fairly new data with all of you. This data is from the Coronavirus Household Evaluation and Respiratory Testing Cohort Study. This is a prospective cohort of households that include children less than 18 years.

The presence of a child in the household is required for enrollment, but all household members are enrolled and followed.

Enrollment is in two sites: one in New York City and the other including select counties in the state of Utah. The cohort includes 1,196 individuals across 300 households, and they were originally enrolled in the fall of 2020. Individuals in the cohort participate in weekly surveillance testing for SARS-CoV-2 infection. In addition to weekly testing that is independent of symptoms, they respond to weekly inquiries about whether they have had any illness symptoms that meet a COVID-like illness case definition.

In addition to their weekly screening with mid-turbinate nasal swabs, individuals also collect an additional swab at the onset of any COVID symptoms. All the viral testing is done via RT-PCR. This slide shows that incident rates of SARS-CoV-2 infection per 1000 person weeks by age group overall and at each site. These are data from September 2020 through

February of 2021. Both sites during this time period experienced a clearly defined single wave of SARS-CoV-2 circulation.

The different colored bars indicate four age groups: children 0 to 4 years, 5 to 11 years, 12 to 17 years, and adults 18 years and older. As you can see here, incident rates were similar across the age groups at both sites and overall among the cohort as indicated.

This slide includes data from FLUTES-C, an ongoing household transmission study in Tennessee and Wisconsin. Whereas the last study I described is a cohort study, this is a case ascertained household transmission study in which lab-confirmed SARS-CoV-2 index cases and all household contacts are enrolled to assess secondary infection rates. The top of the table on the left shows the age category of the primary case or the first case in the household developed illness or to test positive. The numbers of total household contacts are also shown in the first column.

The second column shows the secondary

infection rate of household contacts. In general, the top part of the table captures transmission risk from various age categories. As you can see, the secondary infection rate for primary cases ages 0 to 4 was 46 percent. Secondary infection rates for household members where the primary case of 5 to 11 years is 64 percent.

The third column in the graph on the right shows the risk ratio of secondary infection rates for each age group relative to the reference group, age 18- to 49-year-olds. As you can see, there's not a statistical difference between secondary infection rates for children primary cases relative to adult primary cases. The bottom part of the table captures ages of contacts in their secondary infection rates, somewhat analogous to the last study we described. And, as you can see here, there's no statistical difference between secondary infection rates for child contacts compared to adult contacts.

This slide is from an early field epidemiology household transmission investigation that was done in

Utah and Wisconsin. This slide compares the presence of symptoms in children and adults with COVID-19 after household exposures. By way of disclosure, the age categories here do group all individuals less than 18 years into one category.

But, as you can see, in general, younger children and adolescents have less symptomatic illness when infected with SARS-CoV-2 than adults. Children have more upper respiratory symptoms, largely driven by rhinorrhea and runny nose, but they have significantly less lower respiratory symptoms. The same pattern with children being less symptomatic has definitely held up through several studies throughout the pandemic.

Let's transition and talk a little bit more about hospitalizations. We also see that children have lower hospitalizations than adults of all ages. This graph shows the number of new COVID-19 hospital admissions per 100,000 population, stratified by age. The yellow dotted line shows 0 to 17 years. The solid black line shows the total for all ages, and the purple line at the top shows the hospitalization rates for

those 70 plus years.

The graph on the right shows children and adolescent hospitalization rates placed on a different y-axis than the graphic on the left. The y-axis for the graph on the right showing children 0 to 17 years is over a scale of magnitude lower than the graphic on the right.

This slide shows disaggregated rates of hospitalization for children and adolescents, and it's from the MMWR that was just published last week. In short, it shows hospitalization rates for children and adolescents throughout the pandemic by using CDC's COVID net hospitalization surveillance data. The y-axis shows hospitalization rates per 100,000 populations and the x-axis shows the calendar weeks throughout the pandemic. Ages 0 and 4 are shown in the solid blue line. Ages 5 to 11 are shown in the wide dashed line, and ages 12 to 17 are shown in the narrow dashed line. As you can see, younger children and those between 0 and 4 years and adolescents between 12 and 17 years had higher hospitalization rates compared

to children 5 to 11.

Furthermore, we also have looked at seroprevalence data by age. In summary for this slide, CDC is partnering with commercial laboratories to conduct and publish results from large-scale geographic seroprevalence testing that uses deidentified clinical blood specimens from all 50 states, D.C., and Puerto Rico. They use these residual specimens for SARS-CoV-2 antibody testing. The survey includes people of all ages because we had blood specimens tested for reasons unrelated to COVID, such as routine or sick visits in which blood was collected and tested by one of three private commercial labs across the 52 sites.

The data presented here is from the latest round of testing, covering the period from February 15th through March 21st, 2021. These are anti-nucleocapsid estimates and, therefore, do not take into account vaccination-induced seropositivity. The data shown here is available on CDC's website, and it's updated regularly as testing is scheduled to continue throughout the rest of this year.

As you can see, seroprevalence among children and adolescents 0 to 17 years is actually the highest among all age groups. Notably, although a finer age band illustration is not presented on this slide, they have assessed this, and a manuscript for publication is currently under development. Importantly, when we look at children 0 to 11 years versus children 12 to 17 years, both age groups have approximately the same seroprevalence. Or put another way, younger children's seroprevalence is similar to that of older children and adolescents in this most recent survey.

Taking all the epidemiologic differences I just reviewed and incorporating the evidence, CDC has created a model that estimates the burden of SARS-CoV-2 by age and different disease outcomes within the U.S. during the pandemic to date. The goal of these age-specific burden estimates are to better approximate the true number of cases, symptomatic illnesses, and hospitalizations to date. Age categories are listed in the first column on the table, followed by the point estimates and uncertainty intervals for rates of

infection, rates of symptomatic illness, and rates of hospitalization. All of the rates shown are per 100,000 population.

As you can see infection rates in children 0 to 4 are estimated to be lower than older children and adults. However, school-aged children and adolescents between the ages of 5 and 17 have had infection rates similar to those in some of the adult-aged category. When looking at symptomatic illness, you can see a similar pattern. Rates of symptomatic illness in children 0 to 4 are lower than older children, adolescents, and adults. Children and adolescents between 5 and 17 have an infection rate similar to those in the adult-aged categories.

Importantly, hospitalization rates among children, including younger and older children, are lower than all of the adult-aged categories. Of note, these estimates are updated regularly as we gain more data and are publicly available also on CDC's website. Patterns in the burden estimates will change with time as other public health policies evolve. An important

example of this may be variable vaccination across different age groups.

I want to transition and talk a bit more about a specific severe clinical 19 [sic] outcome or Multisystem Inflammatory Syndrome in children. Multisystem Inflammatory Syndrome in children's an illness in persons aged less than 21 years is characterized by fever greater than 38 degrees Celsius, multisystem organ involvement, lab evidence of inflammation, and a current or recent diagnosis of SARS-CoV-2 infection or exposure with no alternative plausible diagnosis.

By way of history, MIS-C was first identified in April of 2020 in a cluster of children in Europe who experienced hyperinflammatory shock following SARS-CoV-2 infection. In May of 2020, CDC developed a case definition, published a health advisory, and requested suspected cases of MIS-C in the U.S. to be reported to the Health Department. Since then, 51 jurisdictions have reported MIS-C cases to CDC. CDC's been working to summarize the cases reported to our national

surveillance system to better describe and understand MIS-C. And this data included what has been reported through, I think, May of 2021.

So since May of 2020, CDC has received reports of 4,118 confirmed cases of MIS-C in the U.S. with onset between February 19th, 2020, and May 18th, 2021. Shown here is the epidemic curve plotting the seven-day moving average number of MIS-C cases represented by the solid line and COVID-19 cases represented by the dotted line. The left y-axis defines the number of daily average MIS-C cases in units of five. The right y-axis defines the number of daily average COVID-19 cases among all ages in units of 50,000. The grayed-out area on the right side of the figure represents the most recent three-week period for data of which reporting is still incomplete. Cases of MIS-C have occurred in three waves, and you can visually see the peaks of MIS-C following the peaks of COVID-19 infection.

The median age of MIS-C cases is nine years. The graph on the right shows the distribution of MIS-C cases by age. 60 percent of the cases are male. And

among the patients with complete race and ethnicity information, 32 percent are Hispanic/Latino and 30 percent are non-Hispanic Black. 37 percent of MIS-C cases reported a pre-existing condition, and obesity and chronic lung disease were the most frequently reported.

So let's quickly summarize all of this. Here are the highlights of what I have presented. As of June 4th, there have been over 33 million cases of COVID-19 and almost 600,000 deaths in the United States. Children have lower rates of hospitalization and mortality compared to adults. Children are susceptible to SARS-CoV-2, though younger children with infection tend to have fewer lower respiratory symptoms compared to adults.

From prospective cohort and household transmission studies, infection rates are similar across age groups; children can transmit SARS-CoV-2 to others and with similar efficiency as adults. MIS-C is a severe complication of SARS-CoV-2 infections and has had varied clinical presentations. And finally, MIS-C

is highest and disproportionately so among Black and African American children and Hispanic and Latino children. And with that, thank you very much.

DR. ARNOLD MONTO: Thank you very much, Dr. Kirking. I see Dr. Gans has her hand raised. Dr. Gans.

DR. HAYLEY GANS: Thank you very much. I appreciate your presentation, and I really appreciated you giving us that comprehensive sort of history on pediatrics.

I had a couple of questions because I think you pointed out a very important aspect of the data and that we can't clump these age groups together. I think that a little more granular data needs to be, if you have it, provided particularly if you take the -- so the zero to five year or less than five year, whatever, zero to four, also I think, is too aggregated. And so, if you could take the newborn data out of that -- because we know that there is a lot of newborn disease related to parental disease -- if you take that out, can you really discuss what actually the rates are in

that age group without that and any predictions as the adults in the childbearing age actually are vaccinated and obviously wouldn't expose their newborns? That's my first question.

My second question is can we get a little more granularity about the one-year-olds? There was some early data showing actually a higher rate of intensive care use in that group, and it was not clear if that was just severity of disease or discomfort with these young children who were known to be infected with SARS-CoV-2 because I think that's going to be very important as we understand vaccination in these very young children. Thank you.

DR. HANNAH KIRKING: Yeah, thank you for the questions, and we spent a lot of time talking about them here largely because the issue of disaggregating age versus having numbers to show relative patterns has been an ongoing challenge. I will admit that I don't know that I have a strong answer to your question right today in terms of disaggregating the zero to four age group specifically. I will have to check with

colleagues and see how much they've looked at the newborn disease versus the older part of that age cohort and see how much more we can kind of tease out of it.

Part of the challenge is, in our large-scale surveillance data at least, getting the more granular details, but we always wanted as clinicians to understand or be able to make sure it's standardized across the reporting is a lot harder than it might seem. But, yes, I totally appreciate the need for even further age disaggregates, and we'll share that back.

We are talking a little bit across our epi taskforce here at CDC about pushing across the board. You know, obviously, we don't produce all of the data -- but pushing for more finely disaggregated data because anyone working in pediatrics knows that, yeah, a newborn is not a four-year-old and a one-year-old is not a four-year-old, especially when it comes to respiratory viruses.

DR. HAYLEY GANS: Thank you so much.

DR. ARNOLD MONTO: Dr. Hildreth.

DR. JAMES HILDRETH: Dr. Kirking, first, thank you for this great overview and summary. What does the data look like when you look at children with underlying conditions like obesity or asthma or sickle cell? Do the numbers change when you take that into consideration? And could it be that the underlying conditions in minority children are related to them having a higher rate of MIS Syndrome? Is that possible?

DR. HANNAH KIRKING: Could you repeat that last part of the question, Dr. Hildreth?

DR. JAMES HILDRETH: Well, I was wondering whether or not underlying conditions were related to the higher frequency of Multisystem Inflammatory Syndrome in minority children.

DR. HANNAH KIRKING: Yeah, that's a great question. I think to your earlier question, children that do have comorbidity are higher risk. So it's not particularly surprising that's holding true from the other respiratory viruses that we're more familiar with, as well as in COVID-19.

In terms of the relationship between you said with, say, race and ethnicity, comorbidities, and MIS-C, I think there's a complex relationship there that we're still working to understand. The first question I think that we've received a lot is are the higher rates of MIS-C in some of the racial minorities that we see -- is that related to their risk of infection alone? Or is it something on top of just infection or incidence in that population? Initially, there wasn't a lot of data in there, but there is a paper coming out that said we're looking at our surveillance data more broadly -- coming out today actually -- I didn't cover it because it's embargoed. But, in short, it'll show and suggest that, even if you correct for increased incidence rate in Latino and Black and African American children, it seems like the increased burden of MIS-C, or it might be something additionally on top of that.

DR. JAMES HILDRETH: I see.

DR. HANNAH KIRKING: I'm not sure how much we've been able to stratify to see how much of that might be accounted for by comorbid medical conditions,

like you suggest. Definitely, I will take that back to the individuals leading that part of it. I don't know that we have the numbers yet to say strongly that we can stratify by all three of those different things.

DR. JAMES HILDRETH: Thank you.

DR. HANNAH KIRKING: Sure. Of course.

DR. ARNOLD MONTO: Well, Dr. Meissner. And I'd better warn everybody we're going to have to restrict the questions in a little while because you're really running over. Dr. Meissner, please.

DR. CODY MEISSNER: Yes. Thank you, Dr. Monto. Thank you, Dr. Kirking, for such an interesting presentation, and thanks to you and everyone else at the CDC who is providing such remarkable data.

The question -- I guess it's more of a comment rather than a question -- if I look at the most recent rates of hospitalization among individuals under 18 years of age -- and this is at the CDC site -- the rate is 0.4 per 100,000. That means four per million, and the MMWR report that you cited ends on April 24th. If you look at the slope of the curve since April 24th,

the number of hospitalizations is going down quite dramatically.

So I very strongly believe we need a vaccine for adolescents and children, but I want to be sure that the risk of the vaccine is less than the risk of hospitalization because four per million certainly does not constitute an emergency, and there are significant questions about the safety of this vaccine. So maybe you could comment about what's happened in the six weeks since that MMWR report.

And I will also note that MIS-C, if I could read your table correctly, is getting pretty close to zero cases. So as we generate herd immunity, this disease is disappearing between the vaccine and natural immunity. So just playing the devil's advocate here, I think we need a BLA before we can approve this for children. But how would you respond?

DR. HANNAH KIRKING: Yeah, I was kind of expecting this question because I think it's the million-dollar question right now. I think broadly you described the patterns of hospitalization and MIS-C

that, as case counts are falling, those are also falling rapidly for children. So it is not a big surprise in that.

I think the challenge for me as I grapple, you know, and as a -- by the way, background, I'm internal medicine and pediatric trained -- both, but I'm making some of these comparisons throughout the pandemic. But I think the thing that's a challenge for me is that you have a risk-benefit ratio on an individual level and a risk-benefit ratio on a population level. And so I'm not sure where the balance is with how you triangulate both of those considerations.

As case counts fall, the negative outcomes from COVID virus itself, whether that's cases, hospitalizations, MIS-C, are also falling. Having said that, there's no guarantee that the current general case counts that we're seeing in the U.S. is going to stay as low as it is right now. We're all hopeful, myself more than anyone, that pattern does continue, but we don't know. There's variables out there of variance, and we can't ignore what's happening outside

the U.S. and how that may or may not impact our curve here. So we'll see on that.

I think the thing that epidemiologically I also have to consider are not just the risk benefits from a medical standpoint, but there's also kind of the societal risk-benefit, too, of what role children play in the overall pandemic across society. So how to balance that, I think, is much harder, and, as I was trying to think about this presentation, I don't know that there's a precedent for something like this and the question that you all are grappling with right now. Things that I would think about would be, as children return to school increasingly, whether vaccinated or unvaccinated and the importance of other mitigation measures, I do think there are some risks for transmission in any pool of people that are not vaccinated, but that risk is related to background community rates as well.

So it's a little bit of a moving target. But in addition to health outcomes, vaccine outcomes, the big outcome such as keeping schools open and having

childcare available for the rest of America and that's the part that I think is tough. So I appreciate but the risk-benefit ratio for the individual is rapidly changing, and then that's a vital one as well but with some question mark of what could happen in the upcoming months. Sorry, I don't know that I have the magic answer. But that's how I'm thinking about it in my mind.

DR. ARNOLD MONTO: I don't think anybody has the magic answer. One more question and, Dr. Kirking, could you be sure to hang around until this afternoon when we have our general discussion. I'm sure there are going to be more questions about risk as we tackle risk-benefit. So just one more question right now from Dr. Levy.

DR. OFER LEVY: Hello and thank you for your presentation. A few things briefly, I'd like to agree with Dr. Hayley Gans that it's very important to get more granularity on the pediatric data. I know you're limited by what's captured, but this is a plea that we partner in the future to capture with more granularity

the pediatric, the child immune system (audio gap) is changing across days, let alone weeks, let alone months and years. So just to have it in years of life really does a disservice.

As we know, if we take sepsis as an example, you take adult sepsis criteria, apply it to school-aged kids, you miss a lot of sepsis. You apply the pediatric, school-aged sepsis criteria to newborns, you miss all of the sepsis. So there's really an ontogeny here, a change with age and the immune system, and we've got to really be more granular in capturing that. And that would be, I think, within the spirit of the Pediatric Research Equity Act, or PREA, which is alluded to in the briefing document. So I just wanted to put that out there.

The other thing is you talked a little bit about seroprevalence. Did those seroprevalence studies take into account that the pediatric response to infection with SARS-CoV-2 is distinct? Children amount to a different type of antibody response that's narrower but tends to have fewer antibodies and fewer

types of antibodies. So those conventional sera assays might not capture all of the pediatric infection, and we might just be catching the tip of the iceberg.

DR. HANNAH KIRKING: Yeah, thank you for the comments, definitely noted on the age disaggregation and trying to get finer age groups. I 100 percent agree with that, and, like I said, we had a lot of discussion even upcoming to this presentation to get as granular as we could and for sure this desire to even go further. In terms of your second question -- remind your second question. My apologies.

DR. OFER LEVY: It was with seroprevalence. There's work by Dr. Farber and others published in prominent journals saying that children mount a different type of antibody response to this infection, and the conventional assays don't always pick it up.

DR. HANNAH KIRKING: So I would wholeheartedly say that there is truth to that, and that you know, these seroprevalence surveys are for sure trying to recognize the pattern and show the signal. I would not hang my hat heavily because there's still a lot more

unknowns of what's not captured. Seroprevalence survey of a good sample population is not perfect using a nucleocapsid antibody test. On the CDC website, there is a link to the broader data and to the methods that that estimate includes. But I do agree with you. I think it might not be telling the whole picture due to differences in the immunologic response in adults and kids.

DR. OFER LEVY: And finally, we don't know too much about the long-term effects of the infection in children. They might not manifest acute symptoms, but there's more to be learned. Wouldn't there be more to be learned about the long-term effect of this infection early on?

DR. HANNAH KIRKING: Absolutely. (Inaudible)

DR. OFER LEVY: Thank you.

DR. ARNOLD MONTO: Okay. Well, thank you all, and thank you, Dr. Kirking, and please hang around for this afternoon. We're going to have a vigorous discussion related to risk. Next, I'd like to ask Dr. Shannon Stokley from the Associate Director of Sciences

Office at CDC to talk briefly about operational aspects.

CDC: OPERATIONAL ASPECTS

DR. SHANNON STOKLEY: Thank you and good morning and thanks for this opportunity to talk about the implementation of COVID-19 vaccination for adolescents in the United States.

So, as you're aware, after the FDA approved the expansion of the emergency use authorization for the Pfizer-BioNTech vaccine to be used for adolescents aged 12 to 15 years, the Advisory Committee on the immunization practices met on May 12th and voted to recommend this vaccine for this age group. And the recommendation was also published in the *Morbidity and Mortality Weekly Report* and clinical considerations for use of the vaccine were posted on the CDC website.

So, with the approval of the vaccine for adolescents, we wanted to promote vaccination for this age group as quickly and equitably as possible, and we

did this using a multi-pronged approach. So the plan started with relying on the existing infrastructure, such as mass vaccination sites and pharmacies, to open up their appointment systems to include adolescents. This is followed by strategically enrolling primary care providers as COVID-19 vaccine providers. And then finally, we planned to apply school-focused strategies, such as school-located vaccination clinics during the last summer and early fall as children prepare to return to school. And while I present this as a phased approach, in reality, in most states, these activities are being implemented concurrently.

With a planned approach, primary care providers are very important as they are trusted by families and are usually the place where children receive their routine vaccines. Parents have confidence in their providers and prefer for their children to be vaccinated in this setting. However, there have been challenges with enrolling providers because of the packaging of the vaccine, especially for the Pfizer vaccine.

Many sites are not able to handle the minimum order size of 1,170 doses or the newly available packs of 450 doses because their patient volume may be too small. So, unless the packaging becomes smaller or jurisdictional immunization programs are able to break down the package and redistribute vaccine in smaller quantities, many providers are not interested in enrolling in the program. This could have implications for future vaccination efforts if the vaccine were to be recommended for younger children, as we know most of them prefer to receive their vaccine in the primary care office.

Pharmacies and HRSA sites such as federally qualified health centers are also very important to implementation, especially in the areas that may be unserved such as rural areas where they may be the only source of healthcare for some people. And lastly, school-based vaccination will be an important strategy for vaccination as children get ready to start the new school year in August and September, especially for children who are not early adopters of the vaccine.

Many states implemented school located vaccination clinics as soon as the vaccine was authorized for adolescents and many more have plans to conduct them in the late summer and early fall.

With the introduction of the vaccine for adolescents, we were frequently asked about consent for vaccination among minors, and the federal government does not have specific requirements for medical consent for vaccinations. This is determined at the state and local levels, so, therefore, healthcare providers must follow their state laws when providing vaccines to adolescents. These laws do vary by state. For example, in one state, a child aged 15 can self-consent for vaccinations. Whereas, in another state, the age of consent may be age 18. Again, providers must follow their state laws and any policy requirements from their own organization when administering the vaccine to adolescents.

So this slide shows progress to date with COVID-19 vaccinations. The line graph shows vaccination coverage by age group with adolescents aged

12 to 15 depicted by the dashed yellow line. And, as of June 7th, over 171 million individuals have received at least one dose of the COVID vaccine. And that is almost 52 percent of the U.S. population. Among adolescents aged 12 to 15, over 3.4 million, or 23 percent, have received at least one dose of the COVID vaccine. It's also worth noting that 39 percent of the adolescents aged 16 to 17 years, shown in the solid yellow line, have received at least one dose.

When the COVID vaccine became available for adolescents, CDC also updated its guidance about the coadministration of the COVID vaccine with other vaccines. So now the COVID vaccine and other vaccines may be administered without regard to timing, and that means vaccines can be administered on the same day or within 14 days of each other. When deciding whether to co-administer other vaccines with the COVID-19 vaccine, providers should consider if the patient is behind or at risk of becoming behind on recommended vaccines, the risk of vaccine-preventable diseases, and the reactogenicity profile of the vaccine.

These updated coadministration recommendations may facilitate catch-up vaccination of adolescents. The pandemic has had an impact on the delivery of routine vaccines in the United States. And we have been monitoring routine vaccine orders through our Vaccines for Children Program. As of June 6th, orders are down cumulatively by 12 million doses compared to what we were seeing pre-pandemic or in 2019. When we look at this by vaccine, we see that vaccines primarily given to adolescents have been the most impacted.

Compared to the pre-pandemic time, vaccine orders are down 18 percent for Tdap and HPV vaccine and down 12 percent for the meningococcal conjugate vaccine. So, as parents are bringing their children in to get a COVID vaccine, we encourage providers to remind them about the importance of staying up to date on routine vaccines. If vaccines can't be given during the same visit, that's fine, but, if not, parents should make follow-up appointments so their child can get caught up if they're behind.

And to help inform parents about the COVID-19

vaccine for adolescents, CDC has developed a lot of materials, both print and digit. We have specific webpages devoted to the vaccination of teens. We have fact sheets and also a tool kit for pediatric healthcare providers for how to communicate with their patients. And we also have frequently asked questions and other information to dispel myths.

And shown on this slide is just a list of resources that are available and the links. So again, thank you for your attention, and I'm happy to answer any questions you might have.

DR. ARNOLD MONTO: Thank you very much. Any questions? Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Yes, thank you, Dr. Stokley, for your presentation. I have two questions for you. The first is with regard to education of providers. You listed some materials that have been developed for education for patients and parents. But I was curious, because this is such a complex subject with regard to the moving target of the pandemic itself, the epidemiology, and the almost daily sets of

information that come out with regard to vaccine adverse effects and things like that, so what is the CDC doing to prepare providers should they agree and should the packaging change and the vaccine become available in a way that providers can actually get this vaccine in their clinics?

DR. SHANNON STOKLEY: Great question. So part of the onboarding process of when a provider is enrolled as a COVID-19 vaccination provider, there's a requirement for training, and many states have this requirement before they will approve the provider. We have websites with training materials specifically about the vaccine products about storage, handling, administration. Then, there's also materials from the manufacturers themselves that we recommend they view as well. We also have our clinical guidelines website that is updated frequently as things evolve, and it has information to help them with implementing and then administering the vaccine in their practice.

DR. ARCHANA CHATTERJEE: Thank you. My second question is with regard to those resources that have

been developed for patients and parents and guardians, and that is whether they are available in multiple languages that the patients may need those resources in.

DR. SHANNON STOKLEY: Yeah, that's a great question. So we do have resources translated into several languages. I'm not sure of all the languages that are available, but I know we typically have translated information because we know that's important to do for patients to receive information in the language that is their preferred language.

DR. ARCHANA CHATTERJEE: Thank you.

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

DR. STANLEY PERLMAN: Yes, so I just have a short question. In looking at the vaccination rates of the adolescents, is the uptake parallel to the older people in the same geographical areas? Is there any disparity there? Is it just the people -- in the parts of the country that have higher rates of vaccination in total, are those the places that have higher rates of adolescent vaccination?

DR. SHANNON STOKLEY: That's a really good question, and I don't know that I have the answer for that. I know especially with the initial rollout of the COVID-19 vaccine, the older population was prioritized, and we've reached over 85 percent, I think, coverage for adults aged 65 and over. I have not seen analysis done where we've compared a more local level coverage for the older population or adult population compared to adolescents, but that's something we can look into.

I do know that coverage increased pretty quickly for adolescents aged 12 to 15 initially, and we're hoping that that continues over time.

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

DR. PAMELA MCINNES: I have withdrawn my hand. Question answered.

DR. ARNOLD MONTO: Okay. Dr. Gans. Final question.

DR. HAYLEY GANS: Thank you very much. I had just one question about the coadministration. I know the recommendation was highly based on the fact that

obviously individuals who were behind -- and we really want to encourage the usual preventive measures that we have, and I think that that's very, very important. But I wondered if you could talk about actually on the data that actually would have been the basis of those recommendations.

There's not a lot of biological reason that these immunizations necessarily would interfere with other coadministered-in-children vaccinations, however, we have seen obviously in other similar situations where there was some effect on the vaccines that were being given for their routine illnesses. We wouldn't want to interact with that, such as Prevnar with meningococcal, so I think that's it important to realize whether this was data-driven recommendations to catch people up with not a lot of biologic reason and what further information would be forthcoming in this arena.

DR. SHANNON STOKLEY: Yeah, my understanding is the initial guidance around coadministration was following the clinical trials and how they were

implemented. It was not necessarily due to a concern of safety. It was just that's how the vaccine was tested in the clinical trials. But, given that by the time this was implemented for adolescents we've had hundreds of millions of doses administered to adults, there did not seem to be a safety issue. I might defer to Dr. Amanda Cohn, our chief medical officer, to perhaps provide more context for how the decision was made around coadministration. I wasn't involved with that decision.

DR. HAYLEY GANS: Yeah, thank you, and just it wasn't really a safety concern but an immunogenicity concern.

DR. SHANNON STOKLEY: Right. I don't know if Dr. Cohn is available to answer that.

DR. ARNOLD MONTO: Okay. Well, thank you very much. We're going now to post-authorization surveillance activities, and we have a tandem presentation here. First, Dr. Steven Anderson of CBER, FDA, and then Dr. Tom Shimabukuro of CDC. You're on. Thank you very much.

POST-AUTHORIZATION SURVEILLANCE ACTIVITIES

DR. STEVEN ANDERSON: All right. Good morning. As mentioned, my name is Steve Anderson. I'm the director for the Office of Biostatistics and Epidemiology at the Center for Biologics. Today, I'm just going to give a brief update on some of the COVID-19 vaccine safety activities that we've been working on.

We generally divide our activities into passive surveillance and active surveillance. Tom Shimabukuro, who follows me, is going to be talking a lot about VAERS and current updates there. So I won't be presenting on that topic in this presentation, but what I will be focusing on is FDA's work in its active surveillance monitoring programs.

Specifically, we've engaged two sort of data systems: one is FDA is working with the CMS Medicare data in collaboration with the Center for Medicare and Medicaid Services. That's our big claims data system,

and we also have our in-house system which is the FDA BEST system. And for the purposes of this presentation, the focus really is going to be on the claims data because it does have considerable power to be used in vaccine safety surveillance and relevance here.

So, talking just a bit a very brief overview of Medicare data, the first bullet really mentions that it covers 34 million persons is the database that we're using for persons 65 years of age and older. I realize that today's topic is adolescents and children and pediatric populations, so we'll be talking about that in a moment. But I just wanted to mention also aspects of the systems that we're using.

The BEST system, the Biologics Effectiveness and Safety Initiative, uses sort of large claims data systems, as I mentioned, from three large data partners or collaborators. They're large insurers that consist of Optum, CVS Health, and then HealthCore. I just want to mention in advance that they're very important partners in the work that we do, and we really couldn't

do the work without them engaging with us. I just wanted to mention an emphasis in our work on detection of adverse events but also specifically rare adverse events with these large data systems.

Talking about the specific data systems, I wanted to give you a thumbnail sketch of the coverage of these systems. So basically, in the third column, you see the number in millions of the persons covered or number of patients covered in our data system. Overall, those add up to approximately 200 million persons that are covered, and CMS has the bulk of those as you can see. The others -- Optum, CVS Health, HealthCore -- again have tens of millions of patients that they cover.

The important thing, too, about these data is the frequency which would pair up with which they're updated. So, for instance, CMS is updated daily. Optum is sort of every two weeks, and then some are longer. They go to monthly updates.

Just moving onto the next slide, so I think the relevant question for this audience really is how

many doses of vaccines are in these data systems that will be relevant for analyses? So you can see the total numbers displayed here. Just sort of adding them up, I think CMS is 17 million, and the others go between sort of 3 million for Optum, down to approximately 6 million for HealthCore, and 2.6 million or so for CVS Health.

So again, it's slightly less than 30 million doses overall that we have access to for our data analyses. We're actively conducting "near real-time surveillance" in the first two data systems. Obviously, CMS, we've been working quite a while with that, and then Optum just came on in the past two weeks.

I just wanted to mention our near real-time surveillance, and you've heard us talk before at this meeting about the near real-time surveillance or the rapid cycle analysis. We're looking at 16 adverse events, and this approach has been used previously by government agencies during H1N1. So it has sort of a successful track record. And it's been used probably

in each of the last ten years by FDA and CDC for their annual monitoring of the influenza vaccine.

Here are sort of the 16 different adverse events of special interest, and I just wanted to mention initially the choices were made based on adverse events that were previously studied in vaccines but hadn't, sort of, had signals in the preauthorization clinical studies. And now, you can look through and see that some of them that we're looking at, obviously, have now signaled, so for instance, anaphylaxis in the upper left-hand corner. But also, we added thrombosis with thrombocytopenia because of the Janssen vaccine and the cerebral venous thrombosis cases that were identified in the past two months with that vaccine as something we're carefully monitoring.

So those are the sort of types of outcomes we're evaluating, and then this just gives you -- this is a government-wide approach. FDA is working with CDC and the Veterans' Administration. So this gives you a coverage idea of the databases. I just wanted to point

to the bottom, which is those for the pediatric population. So the vaccine safety data links from CDC and the BEST do have coverage for those persons 17 years of age and younger.

So this just gives you an idea about our data sources and their coverage. As you can see, there's reasonable coverage. Again, just various partners, they span from about three to four million total in the populations 17 years and younger, so a reasonable amount of power. Obviously, we'd always like more data, but it's a reasonable amount of power to do analyses.

And then myocarditis is going to be talked about by Dr. Shimabukuro, and we thought we would at least provide some results that we have from our near real-time surveillance for those in both the BEST and CMS systems. So, for BEST, that's the Optum data that we have in persons 12 to 64 years of age. We haven't observed the safety signal. This is probably after one run in the past week, so these are really fresh data, fresh results.

I just also wanted to mention that for the persons 12 to 15 years of age that authorization for the Pfizer vaccine was just made in, I think, the second week of May, and so we wouldn't expect necessarily to see that age population highly represented in the data systems yet. It didn't signal in CMS, as well, for myocarditis and pericarditis, but it's an observation for this outcome that's been observed largely in young persons 30 years of age and even younger. So we didn't expect to see it in the CMS populations, so it's reassuring that it didn't signal in that population as well.

I just wanted to mention, if we do get a signal, the steps we're going to be taking, and that's really going to be conducting more robust epidemiological studies to follow up on any potential signals we identify in the near real-time surveillance program. I just wanted to mention that near real-time surveillance is a nice sort of screening method, but it has a lot of limitations. It really doesn't account for many types of confounding, and so you really need

to launch then a full inferential study if you do signal on something so that you can better understand if that signal is a true positive or not.

I will just point to the SCRI as a self-controlled risk interval analysis, and we're probably going to be relying a lot on that type of methodology for our study. We have studies, sort of, that we're considering obviously for CVST and the thrombosis and thrombocytopenia syndrome, but also myocarditis and pericarditis are also considered for studies in the future. I also wanted to mention the focus on subpopulations in the FDA system, so pediatrics are important to us, pregnant persons, elderly, and other populations.

I just wanted to mention that there's several people involved in this work, probably at least a hundred or so behind the scenes in various contractors and other partners and federal partners. So this work is really a huge effort by many different groups, and I'm thankful for their health and collaboration in accomplishing our safety surveillance work. And I'll

stop there. Thank you so much. I think Tom is going to go directly next.

COVID-19 VACCINE SAFETY UPDATES

DR. TOM SHIMABUKURO: Hi. Can people hear me?

DR. ARNOLD MONTO: Yes, please go ahead.

DR. TOM SHIMABUKURO: Okay.

DR. ARNOLD MONTO: Yes, we can.

DR. TOM SHIMABUKURO: All right. Good morning and thanks for having me. I'm going to be giving some COVID-19 vaccine safety updates. The two topics I'll be covering are early safety data of the Pfizer-BioNTech vaccination in persons 12 to 15 years old and then myocarditis and pericarditis following mRNA vaccination.

So, to start with on the early safety data in 12- to 15-year-olds, I'm going to start off with data from our v-safe system, which is our smartphone-based active surveillance system that uses text messaging and web surveys. We monitor individuals closely: daily

during the 0 to 7 days after vaccination and then weekly up to 6 weeks and then at 3, 6, and 12 months after the last vaccination. These daily surveys during the first week ask about local and systemic reactogenicity and other health impact events.

So, on May 11th, v-safe age limits were expanded to allow registration down to 12 years of age at dose 1, and this is primarily through parents or caregivers. As of May 31st, we had just over 46,000 persons aged 12-to-15 years registered and submitted at least one health check-in during days 0- to 7-day interval after dose 1 Pfizer.

So here's a figure showing the top solicited reactions in younger adolescents compared to older adolescents. So this is looking at local and systemic solicited reactions in 12- to 15-year-olds compared to 16- to 25-year-olds. We chose the 16- to 25-year-old comparator because that's what was used in the clinical trials. And, as you can see, the basic reactogenicity profile of these vaccines are similar in these two age groups. If anything, there's a little less self-

reported local and systemic reactogenicity in the 12- to 15-year-old age group.

Now I want to move onto VAERS data, and, just to remind you, VAERS is our spontaneous reporting, our passive surveillance system -- I'm sorry -- our national system that's comanaged by CDC and FDA. VAERS accepts all reports from anyone, regardless of the plausibility of the vaccine causing the event or the seriousness. Its key strengths are rapid detection of safety problems and the ability to detect rare events. Key limitations are inconsistent quality and completeness of information, reporting biases, and generally an inability to determine cause and effect.

So here's the basic reporting of 12- to 15-year-olds, again looking at 16- to 25-year-olds for comparison both in numbers, and you see the numbers of doses administered. Under there, I don't have this on the slide, but the crude reporting rates are very similar. The breakdown of non-serious adverse events and serious adverse events are also similar between these two age groups.

Here are the most commonly reported adverse events to VAERS after Pfizer-BioNTech vaccination. Looking at 12- to 15-year-olds and again 16- to 25-year-olds for comparison, you can see the most commonly reported adverse events are similar. There appears to be -- and these are the top ten adverse events, and these are not mutually exclusive. You can have more than one adverse event in a report. There may be slightly more adverse events which were indicative of vasovagal reactions in the younger age group, the 12- to 15-year-olds. And these are -- vasovagal are syncope or presyncope-like adverse events but generally fairly similar to the 16- to 25-year-old age group.

So, moving on to myocarditis and pericarditis following mRNA vaccination, I'm going to start off with VAERS data. These are preliminary myocarditis and pericarditis reports to VAERS following mRNA vaccination in reports with dose number documented. So these had to have -- this is limited to where there was a dose 1 or a dose 2 documented. And, by preliminary reports, I mean reports that come to us and we detect

either through a search of MedDRA codes, which is the coding that we use for these reports, or they're pre-screened before they go through the processing procedures. Because they are suggestive of myocarditis, the contractor forwards those to CDC, or, when we're alerted to a report from a healthcare provider out there, we basically take the report then. Or we go in and pull the report all based on information the healthcare provider has given us.

So follow-up, medical record review and application of the working case definition and adjudication is ongoing or pending in many of these reports. These are the preliminary reports. As you can see, there are more reports after dose 2 compared to dose 1, slightly more after Pfizer than Moderna, but there has been slightly more Pfizer vaccine doses administered. Also, Pfizer is the only vaccine that's authorized in these younger age groups.

So these are the characteristics of these preliminary reports, again with a dose number documented. I think the take-home here is that for

reports occurring after dose 2, the median age is slightly lower. The median time to symptom onset may be a bit shorter: two days versus three days. The proportion of male and female reports is different. There is a higher proportion of male reports compared to female reports and the dose 2 reports compared to the dose 1 reports. I will say that these findings and the findings on the previous slide are consistent with the surveillance data that emerged from Israel and also from other case series reports and from the Department of Defense reports of myocarditis after mRNA vaccination.

This analysis is limited to reports in individuals 30 years and under and focuses on the presenting signs and symptoms, and you can see overwhelmingly chest pain was the most common presenting symptom. Some patients do have dyspnea, but chest pain is really the hallmark. As you can see, ST or T-wave changes on an ECG and elevated troponins are common. Also, a number of these individuals have abnormal echocardiography or imaging studies.

Of these 475 reports in individuals 30 years and under -- again, this is an age-limited analysis -- we do have outcomes or disposition on a substantial number of these. So 226 of these 475 reports met the CDC working case definition, and follow-up and review are in progress for the remaining. 285 had a known disposition. 270 had been discharged. 15 were still hospitalized. Of the 270 discharged, 91 percent were discharged home. Of these 270 discharged, the recovery status was known for 221, and 81 percent of these 221 had full recovery of symptoms. And 19 percent had ongoing signs or symptoms or an unknown recovery status.

So this looks at preliminary myocarditis and pericarditis reports to VAERS following just second dose of vaccination, and it's looking at a 30-day observation window. So again, this is limited to second dose -- reports after a second dose where the symptom onset was in 30 days, broken down by age groups. You see the doses administered there in the second column, and, on the far right-hand column, you

have the observed counts. These are the actual preliminary VAERS reports.

The expected value we see in the column just to the left of the observed is based on published literature rates. The crude reporting rate is a simple calculation. You just take the observed, divided by the doses administered, multiplied by a million, and you get the crude reporting rate per million doses administered.

And you can see there's very few reports in the 12- to 15-year-olds, so that data's a little bit difficult to interpret. But, in the 16- to 17-year-olds and the 18- to 24-year-olds, the observed reports are exceeding the expected based on the known background rates that are published in literature. It's a bit of an apples to oranges comparison because again these are preliminary reports. Not all these will turn out to be true myocarditis or pericarditis reports. And the expected are based on published literature.

Of note, of these 528 reports after second

dose with symptom onset within 30 days, over half of them were in these younger age groups, 12 to 24 years old. Whereas, roughly 9 percent of the total doses administered were in those age groups. So we clearly have an imbalance there.

So now I'm going to move onto our data from our vaccine safety data link. This is our population-based system. It's an EHR-based system, so we have complete or near-complete information on our covered population, which includes nine participating, integrated healthcare organizations with data on over 12 million persons per year.

So this is doses administered through May 29th. You can see about 4.8 million Pfizer-BioNTech doses and 4 million Moderna doses. The breakdown between dose 1 and dose 2, the proportions are pretty similar between these two doses, so substantial amount of doses administered in the vaccine safety data link.

This graph looks at the same data although it's broken down by age group, and the take-home message on this is, in these younger groups, 12- to 15-

year-olds and 16- to 17-year-olds, we have limited doses administered, limited exposure in these age groups. We have substantial exposure in the 18- to 49-year-old age group but, again, in these younger, adolescent age groups to date limited vaccine doses administered.

So this is a table -- this actually shows a roll-up of all the prespecified outcomes that we are conducting near real-time sequential monitoring on in the vaccine safety data link. I'm looking at a 21-day risk interval. This is a vaccinated concurrent comparator analysis. As you can see, we've had no statistical signals in our primary analysis for any of these prespecified outcomes. I just want to draw your attention to the myocarditis/pericarditis, which is highlighted. This analysis is adjusted for age by five-year age groups, but this is not an age-stratified analysis. So, while we have not signaled here, the adjusted rate ratio is 0.94. Again, if you remember to the previous slides a bit, there has been limited vaccine doses administered in these younger age groups.

So what we did was we went and conducted an additional age-stratified analysis, and this is outside of the sequential monitoring, the surveillance activity. This is an additional analysis, age-stratified, looking in the 16- to 39-year-old age group and the 21-day risk interval. As we accumulate more data, we will be able to chop those ages up finer, but right now, to get meaningful results, we had to use a fairly wide age interval.

And this is by vaccine type and by dose. You can see on the top there for Pfizer, the overall analysis, the adjusted rate ratio is 0.49, and both of the rate ratios after dose 1 and dose 2 are below one. However, you see this dose effect where the adjusted rate ratio after dose 1 is 0.12 and after dose 2 is 0.84, so there is evidence here of a dose effect.

If you look at Moderna, the adjusted rate ratio overall is four. After dose 1, it's 1.74, and what's really driving that is the dose 2 where we have 11 events in the risk window, and the adjusted rate ratio right now is not estimable. The reason for that

is we have zero events in the control interval.

I will mention that it is early. We are still accumulating follow-up time, so cases moving into the control window can have a pretty substantial impact on the adjusted rate ratio. But right now, there is a substantial dose 2 effect for Moderna, and that is probably driving the overall result from Moderna.

So this slide is just a straight-up rates -- post-vaccination rates, looking at rates after both doses and then after dose 1 and dose 2 for combined and by product type. What you see here, again, is this second dose effect where the rate -- the myocarditis/pericarditis rate per million doses administered is substantially larger after second dose, both in the overall analysis and by product type, both for the Pfizer-BioNTech and Moderna vaccines.

To sum up the findings, the initial safety findings for Pfizer-BioNTech vaccination in 12- to 15-year-olds from v-safe and VAERS surveillance are consistent with the results from pre-authorization clinical trials. Analysis of VAERS preliminary reports

of myocarditis and pericarditis is in progress, including follow up to obtain medical records to complete reviews to apply the working case definition to adjudicate cases. The preliminary findings do suggest that the median age of reported patients is younger, and the median time to symptom onset is shorter among those who developed symptoms after dose 2 versus dose 1.

There's a predominance of male patients in younger age groups, especially after dose 2. I would just mention that myocarditis is more common in males in general. The observed reports exceed expected reports after dose 2 in the 16- to 24-year-old age range. And limited outcome data suggest that most patients had full recovery of symptoms. The early vaccine safety datalink data also suggest more cases after dose 2 versus dose 1, an overall rate of about 16 cases per million after the second dose.

And finally, an ACIP meeting is scheduled for June 18th, next Friday. That time will update the data, further evaluate myocarditis following mRNA

vaccination, and assess benefit-risk balance. Here's some educational materials with their references. I'd like to acknowledge the contributions from the following investigators and their organizations. I'm happy to take questions.

DR. ARNOLD MONTO: Thank you, both, very much. This has become a critical issue, post-approval licensure follow up for these rare side effects that would not be found in the clinical trials even if we went to rather large sizes. Before we get into the multiple questions that are out there, could you tell us, if there is an approval, let's say, down to six months of age, which is on the table, what kind of resources do you have for follow up in young children? I don't know who wants to take that.

DR. TOM SHIMABUKURO: I can. I mean, I can start that, so the VSD has -- and VAERS as a spontaneous reporting or passive surveillance system basically has the entire U.S. population under surveillance. So anyone eligible to get a vaccine could potentially report to VAERS. In those age

groups, it would be clearly through parents, caregivers, or healthcare providers.

Myocarditis and pericarditis is an adverse event of special interest in our monitoring, so we are following up on every report of myocarditis/pericarditis, especially in these younger age groups to get medical records to adjudicate these cases and to confirm cases. In the vaccine safety datalink, our ages go down birth through older adults, so we have coverage on younger individuals -- on children as well.

DR. STEVEN ANDERSON: And then just to follow up in the BEST systems and the data systems that we have, I believe we do go down to six months of age. We definitely go down to one year, but probably six months as well.

DR. TOM SHIMABUKURO: I'll also mention that our clinical immunizations safety assessment project team is a collaboration between CDC and seven medical research centers, and these individuals are available to review complex cases. So complex adverse events

following -- cases of adverse events following immunization in children, we have the ability to work with our collaborators and academia to do deep dives into individual case reports, including for children.

DR. ARNOLD MONTO: Right. And I think the issue is sensitivity, and then you can work it out after you detected some of these putative adverse events. Dr. Kim.

DR. DAVID KIM: Oh, thank you very much. I have a question for Dr. Anderson. You discussed the BEST, as in B-E-S-T, capital letters, as a terrific data source for children, older children as well as younger children. I'd like to ask you, besides CVS, Optum, and HealthCore, are there plans to expand the surveillance database that you currently have to include millions of other potential surveillance opportunities?

DR. STEVEN ANDERSON: Yeah, so we have -- I didn't present that. I think I presented that at a past Advisory Committee meeting. I guess I should have put that slide back in, but the BEST system is really

additional claims systems like market scans and others but then also EHR systems. So we have several EHR systems that we include as well, and some of those are also claims and EHR-linked data systems as well. So that gives us a little bit more granularity of data as well. We can reshare that slide for the Committee just for your information so that you have that.

DR. ARNOLD MONTO: Okay. Dr. Gans.

DR. HAYLEY GANS: Thank you so much for that wonderful data. I had a question that was along the same lines as Dr. Kim. So, when we add in all of the systems of surveillance that are going to be considered moving forward, what percentage of the pediatric population actually is accounted for then when you're considering the BEST and VSD and however BEST is going to be expanded? That's question one.

DR. STEVEN ANDERSON: Yeah, so I don't have that at my fingertips right now, but I can ask my staff, and then we could provide that answer a little bit later, if that's helpful.

DR. HAYLEY GANS: Okay. Wonderful. And along

those lines as for considering some of the particularities and unique features of pediatric disease, we know that there is a lot of immune-mediated diseases that actually aren't on your list of diseases that are being accounted for. There's very specific ones that we're starting to see in the adult population, the thrombocytopenia and things like that. But the disease is actually slightly different in pediatrics in terms of the immune-mediated disease, and, therefore, the reaction to the vaccine might be different. I know that VAERS will account for these and you can pop them into these other systems, but I'm wondering if we can actually just be proactive about looking for those in our nonpassive surveillance -- so in the VST and BEST -- and put those into the list of signals that would be accounted for.

DR. STEVEN ANDERSON: Yeah, so, Tom? So I think from our perspective that we do -- so, I'll just give you an example. So we've developed sort of a little more expanded list of vascular conditions that we're going to be evaluating as well because of the

signal of the CVST and the TTS, and so I think we are considering doing something similar for pediatric conditions, too, because I think, as you mentioned, that there's some nuances. And it's a special population that we really have to consider conditions that are specific to that population -- to the pediatric population.

DR. HAYLEY GANS: Right. And just --

DR. TOM SHIMABUKURO: So we have the -- oh.

DR. ARNOLD MONTO: Thank you.

DR. TOM SHIMABUKURO: We have the ability to add conditions --

DR. ARNOLD MONTO: Go ahead. I'm sorry.

DR. TOM SHIMABUKURO: We have the ability to add prespecified outcomes in VST, and we would certainly work with our colleagues in the FDA to identify outcomes that we may want to consider adding.

DR. STEVEN ANDERSON: And using (inaudible) to provide that advice as well.

DR. TOM SHIMABUKURO: Mm-hmm.

DR. ARNOLD MONTO: Right. Dr. Meissner.

You're on mute, Dr. Meissner.

DR. CODY MEISSNER: Thank you. Can you hear me now?

DR. STEVEN ANDERSON: Yes.

DR. CODY MEISSNER: Yes. I would like thank both Dr. Anderson and Dr. Shimabukuro for fascinating presentations, and, Dr. Shimabukuro, your presentations are always crisp and informative. Thank you both for all of the time that you spent in this critical area.

So I'd like to go back to the myocarditis issue because I think that's going to be very relevant for adolescents and children when we're weighing the benefit of risk. I mean, I can't help but be struck by the fact that it occurs more commonly after a second dose, as a pretty specific interval of time. It's primarily after the mRNA vaccines as far as we know.

We know that there's consistent age. There's a lack of alternative explanations, even though these patients have been pretty well worked up. And it's a widespread occurrence because Israel, as you said, has found a pretty similar situation.

So the question that I would like for you to clarify is can you restate the rates of occurrence of vaccine-induced thrombosis, thrombocytopenia that occurs in women in their 30s and 40s, and the rate that you suggested for the occurrence of myocarditis that's occurring in adolescents and young children?

DR. TOM SHIMABUKURO: So the first question is the rates of TTS in the high-risk strata. Is that what you're asking, Dr. Meissner?

DR. CODY MEISSNER: Yes, sir.

DR. TOM SHIMABUKURO: So the highest rates are in younger women, and I don't remember exactly what the age breakdown is. I believe it's the 30 to 39 and 40 to 49. It ranges from around 11 to 12 per million in that group to around 9 to 10 per million in the 40 to 49.

At this point, I think we're still learning about the rates of myocarditis and pericarditis. We continue to collect more information both in VAERS and continue to get more information in VSD. I think as we gather more information, we'll begin to get a better

idea of the post-vaccination rates and hopefully be able to get better and more detailed information by age group.

I'll say it's still early. The authorization and the recommendation for the 12- to 15-year-olds was in mid-May, and immunization of these older adolescents probably didn't really get going till later in the vaccination program. So we're still gathering information. You know, I believe that we will ultimately have sufficient information to answer those questions. I will mention that there will be an ACIP meeting next Friday where we'll have updated information from the information I've presented today, and that will be put in the context of benefit and risk.

DR. CODY MEISSNER: So the risk of myocarditis in the high-risk adolescents is on the same order of magnitude of the risk of VITT, at least based on our available data. Is that correct?

DR. TOM SHIMABUKURO: I wouldn't be comfortable comparing those two outcomes. They are

fundamentally different outcomes, and I think with TTS, I think we had strong evidence of a causal relationship fairly early on after that vaccine started to be used. I think now we're still gathering information on myocarditis, still assessing the risk, and I think there is still more work to be done and more information and data to be analyzed for myocarditis. I'm not sure that we want to compare those two outcomes -- fundamentally different and really in different age groups and different strata as well.

DR. CODY MEISSNER: Yeah, my thought was should this be included in informed consent? Because there is -- I think it's hard to deny that there's some event that seems to be occurring in terms of myocarditis, so that was my thought, but thank you very much for your answer.

DR. STEVEN ANDERSON: In the Israel study, I think the rate was 1 per 6,000 was recorded and then specifically in that male population 16 to 24 years of age, and that's the posted result. So that at least gives you an idea. That may be an overestimate for our

population, but that gives you a better estimate at least for that population.

DR. TOM SHIMABUKURO: I'll mention on my slides that we do have links to information on myocarditis and pericarditis, both for healthcare providers and for the general public. So we're committed to timely communication and transparency and communication.

DR. CODY MEISSNER: Thank you both.

DR. ARNOLD MONTO: Thank you. There is just time for two more questions. We're already eating into our major question and answer period. Dr. Portnoy.

DR. JAY PORTNOY: Great. Thank you very much for this presentation. It was excellent, and I want to comment about the v-safe program. Because every time I filled out my v-safe thing, I felt really good that I was contributing to the process. It was a really well done and well-executed program.

The question I have is about the rate of these adverse events in patients who had the vaccines, and how does that compare to the rates of the same

reactions in unimmunized individuals who actually get infected by COVID? When I'm talking to my patients about getting the vaccine, they want to know what the risk is of getting the vaccine, but they also want to know what the risk is if they don't get the vaccine and get infected by COVID. So is there a way that you could compare these risks of these reactions to the vaccinated patients versus if you get infected?

DR. TOM SHIMABUKURO: I think what you're getting at is a benefit-risk assessment.

DR. JAY PORTNOY: Yes. Exactly.

DR. TOM SHIMABUKURO: And I'll have to say that that is going to be the topic of the ACIP meeting next Friday where the folks in the epi groups will talk about national disease outcomes and put that in the context of benefit and risk with respect to vaccination.

DR. JAY PORTNOY: Because obviously, vaccines have a risk of adverse events, but, if they're a lot lower than the risk of the infection, then the risk-benefit is still worth getting the vaccine. Thank you.

DR. TOM SHIMABUKURO: Mm-hmm.

DR. ARNOLD MONTO: Right. Finally, Dr. Offit.

DR. PAUL OFFIT: Thank you. This question is for Dr. Shimabukuro. Tom, we also see troponin leak in patients who have MIS-C where clearly that's immune-mediated, and then usually by the time you've seen this, the infection is resolved. That also appears to be true here sort of amplified by the fact it is a second dose rather than -- more of a second dose than a first-dose phenomenon. So, in both cases, it seems to be an immune-mediated effect that's causing myocardial involvement. Do you have any thoughts as to what the pathogenesis of that is, or are we going to wait until the ACIP has this discussion on the 18th?

DR. TOM SHIMABUKURO: There are discussions about the potential pathogenesis of this condition. I can't give you an answer right now on pathogenesis. I do want to say that for the data that we presented, we specifically excluded MIS-C cases because we think that's fundamentally different than these myocarditis cases, which the patients tend to have just

myocarditis, not the other manifestations of MIS-C, and tend to do quite well with conservative treatment.

DR. PAUL OFFIT: Thank you.

DR. ARNOLD MONTO: Okay. Thank you all very much. We're going to take a well-earned break. We'll resume, since we're running about 20 minutes late, at 10:55 Eastern. 10:55 Eastern.

[BREAK]

FDA PRESENTATION – CONSIDERATIONS ON DATA TO SUPPORT LICENSURE AND EMERGENCY USE AUTHORIZATION OF COVID-19 VACCINES FOR USE IN PEDIATRIC POPULATIONS

MR. KAWCZYNSKI: All Right, welcome back. Arnold, take it away.

DR. MONTO: Next we’re going to hear the FDA presentation, Considerations on Data to Support Licensure and Emergency Use Authorization of COVID-19 Vaccines for Use in Pediatric Populations. And we have presenting Dr. Doran Fink of CBER. Dr. Fink.

DR. FINK: Good morning. Welcome back, to the committee, and to members of the public who are watching. I'm Doran Fink. I'm the Deputy Director for Critical Review in the Division of Vaccines and Related Products Application, Office of Vaccines Research and Review, in CBER FDA.

Dr. Monto already introduced the title of my talk, so I'll proceed to the overview for my presentation. This will follow Section 2, of the FDA briefing document for this VRBPAC meeting, very closely. I'm going to begin by discussing some general considerations for development of vaccines in pediatric populations, and data to support licensure or emergency use authorization, as these data might apply to COVID-19 preventive vaccines.

The second part of my talk will then address specific considerations for data to support licensure or emergency use authorization of COVID-19 vaccines for use in adolescents and in younger pediatric age groups respectively.

As Dr. Naik mentioned in his introductory FDA

talk this morning, there is intense interest in pediatric development of COVID-19 vaccines. This interest is not only due to public health concerns, but also because addressing pediatric development of COVID-19 vaccines would be a legal requirement for any vaccine manufacturer pursuing licensure in the U.S.

As required by the Pediatric Research Equity Act, or PREA, a vaccine manufacturer applying for FDA licensure of a COVID-19 preventive vaccine would need to provide, at the time of the licensure application for use in adults and for all pediatric age groups from birth through less than 17 years, one of the following: either assessments of vaccine safety and effectiveness, from clinical trials in pediatric subjects or other sources; or, a request for deferral of studies to assess vaccine safety and effectiveness in pediatric age groups to be completed at a later date; or, request for a waiver, with an appropriate justification, from the PREA requirement to provide these assessments.

Now, those of you who are astute observers will probably recognize that PREA covers age groups

from birth through less than 17 years. However, we are asking the VRBPAC to focus their discussion today on pediatric age groups from six months to less than 18 years of age.

Why the differences? Well, first of all the typical development plan for vaccines in transition from adult development to pediatric development typically includes a cutoff at 18 years of age. So even though the upper age limit that is covered by the Pediatric Research Equity Act is less than 17, we're going to follow the trajectory of typical pediatric vaccine development, up to age less than 18 years.

At the lower end of the pediatric age range, PREA covers down to birth. However, there are some specific considerations for younger infants, birth through less than six months of age, that are particularly complex. For example, it's possible that maternally derived antibodies transferred via the placenta could provide protection in infants following either vaccination of pregnant women, or natural infection of women of childbearing potential.

Secondly, for pediatric development of vaccines for use in very young infants, there's the need to considered concomitant administration with multiple and very closely staged routinely administered immunizations.

Finally, the typical age de-escalation approach to pediatric development starts with the oldest age groups, i.e., adolescents, and then proceeds downward, carefully evaluating for vaccines safety and also dose ranging to ensure the doses studied in pediatric age groups are well tolerated. Thus, the youngest age group of birth to less than six months of age, if pediatric development proceeds in that age group at all, is typically the last to be initiated. At this time we're not aware of any studies that have been initiated involving infants less than six months of age.

So, because of the need for further discussion about trial design and other specific considerations for this youngest age group, we are, therefore, going

to focus our discussion starting with six months of age.

We're going to cover both data to support licensure, as well as data to potentially support extending an emergency use authorization of a COVID-19 vaccine for use in pediatric age groups, prior to licensure of the vaccine for use in those age groups.

Extension of an emergency use authorization for pediatric age groups could be considered as needed to address the ongoing (inaudible) COVID-19 public health emergency. However, such an extension would rely upon a determination that all statutory criteria for emergency use authorization are met. Including that there are sufficient data to support the vaccine's known and potential benefits outweighs its known and potential risks in the age group, or age groups, being considered for emergency use authorization.

And so consistent with FDA's approach to emergency use authorization, as outlined in our guidance document, an emergency use authorization for use in millions of healthy pediatric vaccine recipients

would rely on data from at least one well-designed clinical trial that demonstrates the vaccine's safety and effectiveness in a clear and compelling manner.

And to reiterate, today VRBPAC is asked to discuss general considerations for safety data, specifically safety data to support licensure or emergency use authorization of COVID-19 vaccines for use in pediatric age groups from six months to less than 18 years.

We recognize that the universe of considerations around pediatric COVID vaccine development, licensure, and emergency use authorization is not limited to safety data. However, to focus the discussion, we are asking that the VRBPAC not discuss product specific considerations, including data to support initiation of pediatric trials for specific COVID-19 vaccines, or approaches to enrollment of specific age groups. These are discussions that FDA is having, and are ongoing, with vaccine manufacturers, and reply upon the protections afforded by federal regulations for protection of pediatric research

subjects.

We also recognize that for public health and practical reasons, there is intense interest in developing data to inform concomitant use of COVID-19 vaccines with other vaccines that are routinely recommended for use in pediatric populations.

We could not agree more with the importance of these data, and therefore, we encourage vaccine manufacturers to develop these data in their pediatric studies. However, in keeping with regulatory precedent, data to inform concomitant use of COVID-19 vaccines with other routinely recommended immunizations would not be a requirement to support either licensure or emergency use authorization for use in pediatric age groups.

I'd like to turn now to some more specific considerations regarding demonstrating vaccine effectiveness and demonstrating vaccine safety in pediatric populations. As outline in the VRBPAC briefing document, there are several potential options for demonstrating vaccine effectiveness in pediatric

populations.

One option is a clinical endpoint efficacy trial in which the effectiveness of the vaccine is directly demonstrated for preventing SARS-CoV-2 infection and/or disease. The briefing document goes into some detail about various considerations for endpoints and success criteria for (inaudible) efficacy trials. However, FDA acknowledges that, based on current COVID-19 epidemiology, conducting clinical endpoint efficacy trials that are adequately powered for formal hypothesis testing in pediatric population, specifically in those age groups for which disease incidents is lowest, may be very difficult if not infeasible.

Therefore, my presentation will focus on the second option, which is the immunobridging trial. This is a well-established approach to demonstrating effectiveness in pediatric age groups, based on first of all, prior demonstration of vaccine efficacy in a comparative population, typically adults, followed by comparison using statistical hypothesis testing, in a

very rigorous manner, of immune responses elicited by the vaccine in a pediatric age group as compared to the group in the population in which vaccine efficacy has previously been demonstrated. This immunobridging approach presumes that disease pathogenesis, the mechanism of protection, are similar across the age groups being compared.

Now, clearly COVID-19 disease outcomes are different between pediatric age groups and adults and even across pediatric age groups. And there may be differences in SARS-CoV-2 and COVID-19 vaccine immunology across age groups. However, based on available data, FDA considers that mechanisms for disease pathogenesis and protection elicited by COVID-19 vaccines are sufficiently similar across age groups to allow for this immunobridging approach.

Immunobridging trials should be adequately powered to demonstrate statistically non-inferior immune response in the pediatric age group being evaluated as compared to the group in which vaccine efficacy was previously demonstrated.

As an example of a comparative group, my presentation list adults 18-to-25 years of age. We would typically support use of a younger adult age group, as opposed to for example elderly adults being included in the comparative population, to mitigate against bias that would favor a more robust immune response in a younger population (inaudible) pediatric age group that could bias the study in favor of success.

Immune response biomarkers that are selected for immunobridging trials should be clinically relevant to the disease process, and, to the suspected or demonstrated mechanism of protection. However, they do not need to be established scientifically to predict protection against infection or disease at a given threshold.

We have a number of examples of previous vaccines that have been approved for use in pediatric populations, based upon immunobridging, using immune response biomarkers that have not been established to predict protection against infection or disease at a

given threshold. Some examples that were mentioned in the briefing document include HPV vaccines and oral cholera (inaudible) vaccine.

Based on currently available data, FDA considers the neutralizing antibody responses can be used for immunobridging trials of COVID-19 vaccines. And we would consider that these trials should evaluate both geometric mean titers and seroresponse rates, to evaluate the full range of neutralizing antibody responses with seroresponse rates evaluating the lower end of the response range, and geometric mean titers evaluating the higher.

Of course, if an immune response biomarker were established to predict protection at a given threshold, then an immunobridging trial could proceed based on evaluation of seroresponse rates alone. And in this case those seroresponse rates would be seroprotection rates.

Now even though we recognize that it may be difficult, if not infeasible, to conduct an adequately powered clinical endpoint efficacy trial with formal

hypothesis testing, an immunobridging trial should plan for efficacy endpoint analyses as feasible to support the immunobridging data. These clinical endpoint efficacy analyses can be descriptive. They don't need to involve formal statistical hypothesis testing.

FDA would expect that any immunobridging trial, designed to support either licensure or emergency use authorization of a COVID-19 vaccine in pediatric age group, be scientifically rigorous as is our usual standard for data to support pediatric use of any preventive vaccine.

Here are some features of scientifically rigorous pediatric immunobridging trials. First of all, we would expect that the pediatric and adult comparator groups are similar with respect to demographic variables, other than age. And as I mentioned on a previous slide, the age differences should be minimized to the extent possible. They should be similar with respect to baseline health status. And they should be similar with respect to prior exposure to SARS-CoV-2 infection or vaccination.

For the cleanest data ideally both groups, the pediatric group and the adult comparator group, would be naïve to both SARS-CoV-2 infection and vaccination. We recognize, given the trajectory of the pandemic and uptake of COVID-19 vaccines, it could be very difficult to conduct a trial in which a naïve pediatric group is enrolled concurrently with a naïve adult comparator group. And for this reason, the comparator group does not necessarily need to be enrolled concurrently in the same trial with the pediatric group being evaluated, as long as there are adequate measures in place to mitigate against introduction of bias in terms of selection of participants and conduct of the immunogenicity assays and analysis.

We would expect that a sufficiently stringent statistical success criteria be used. And, typically, what FDA has accepted for immunobridging trial would be non-inferiority margins of 1.5-fold for geometric mean titers, and -10 percent for seroresponse rates. We are open to the possibility of alternative statistical success criteria, but only if adequately justified.

Finally, we recognize that pediatric development will necessarily involve ensuring that dosage evaluated, in pediatric study subjects, are safe and well tolerated. And, therefore, a dose escalation approach, that would be typical of pediatric development, would also typically be accompanied by dose ranging to select a dose that is well tolerated in a given age group.

When contemplating an immunobridging approach to infer effectiveness, not only in a different age group than that for which the vaccine has been demonstrated to be effective, but also at a different and likely lower dose level, we would need to ensure that the data to support the use of the selected immune biomarkers are sufficient that we have sufficient confidence in those data to support the immunobridging approach, not only to a different age group but also to a different dose level.

Once again, this does not necessarily mean that we would require an immune marker that is established to predict protection at a given threshold.

This would not necessarily be a requirement.

I would like to turn now to evaluation of vaccine safety. And, as stated in our June 2020 guidance on development and licensure of vaccines to prevent COVID-19, the general approach to safety evaluation of COVID-19 vaccines should be no different than for other preventive vaccines for infectious diseases. And this is true for pediatric populations as well.

We would expect that pediatric vaccine trials with COVID-19 vaccines assess common injection site and systemic adverse reactions that would be solicited for at least one week after each study vaccination. We would expect that such trials would collect and evaluate all adverse events for at least one month after each vaccination. And that they would evaluate all serious other medically attended adverse events, and adverse events of special interest, which would include cases of severe COVID-19 and MIS-C should they occur, collected for the duration of the study.

The study duration should be at least six

months and ideally one year or longer after the last vaccination. And current pediatric COVID-19 vaccine trials in progress are operating consistent with this expectation.

Finally, we would expect inclusion of a comparator group for safety, ideally one that receives a placebo control, followed for as long as is feasible. We recognize that some adverse reactions, for example, myocarditis or pericarditis as discussed earlier today, may be too infrequent to detect in a safety database of typical size for pre-licensure clinical trials, even a safety database that includes tens of thousands of pediatric trial participants.

COVID-19 vaccines represent a novel class of preventive vaccines, with some candidates also representing novel vaccine platforms. Consistent with our approach to other vaccines for infectious diseases, we would expect an overall safety database for pediatric age groups from six months to less than 18 years to generally approach approximately 3,000 trial participants vaccinated with the age-appropriate dosing

regimen intended for licensure or authorization and followed for at least six months after completion of the vaccination regimen.

This is a general consideration and does not account for any specific safety concerns that might arise during clinical development either in adults or in pediatric age groups that would warrant evaluation in a larger pre-licensure safety database if feasible.

Now, Dr. Meissner, earlier in the day asked a question about pediatric safety databases for other recently approved vaccines in the U.S. And, I'll reiterate here that in cases where there's been available data in a large number of adults and an immunobridging approach has been used, to support and demonstrate effectiveness in pediatric populations, the pediatrics safety database that FDA has accepted is consistent with what is outlined on this slide.

In the example of Gardasil, the first FDA approved HPV vaccine, the pre-licensure safety database for ages nine to 17 years was slightly over 3,000. And this was an approval for use in that pediatric age

group that was concurrent with approval for use in young adults ages 18 through 26. So at that point we didn't have much in the way -- we didn't have anything in the way of post-licensure safety data in adults. For other vaccines that have FDA approval for use in pediatric age groups, based on immunobridging to infer effectiveness, we have allowed a pediatric safety database of considerably less, around 1,500 for Japanese encephalitis vaccine, and slightly more than 500 for oral cholera vaccine.

Regardless of the overall size of the pediatric (inaudible) (audio skips) safety database, we would not necessarily expect the entire safety database to be available for FDA review at the same time. As I mentioned before, pediatric development typically follows an age de-escalation approach that allows for safety data and dose ranging in order age groups to then inform selection of an appropriate dose for younger age groups.

So FDA had in the past, and would for COVID-19 vaccines, consider age group specific safety data for

either licensure or emergency use authorization, if appropriate, based on benefit/risk considerations. There would need not involve review in consideration of the entire pediatric safety database from six months to less than 18 years at the same time.

However, this overall safety database should include adequate representation across age groups, especially younger age groups that are less physiologically similar to adults. And we would expect an adequate number of vaccine recipients in each specific age group, and I will get into that in a later slide.

In addition to pre-licensure clinical trials safety data, we would also base any licensure or emergency use authorization decision on data that also considers safety experience from clinical trials and post-licensure and/or post-authorization use in older age groups. For example, younger adults for use in adolescents, and younger adults and adolescents for use in younger pediatric age groups. These safety data in older age groups would be considered in the risk

assessment for each pediatric age group.

That finishes my discussion of general considerations, and so now I'm going to turn to more specific considerations for licensure or emergency use authorization of COVID-19 vaccines for use in specific pediatric age groups, starting with adolescents.

We would expect that evidence of effectiveness, for use in adolescents, be derived from an immunobridging trial that is adequately powered and that also include descriptive clinical endpoint efficacy data as available.

A safety database that could support licensure for use in adolescents would include at least a thousand younger adolescents, i.e., those 12 to less than 16 years of age, and additionally, up to several hundred older adolescents, i.e., those 16 to less than 18 years of age, each with a median follow up of six months after completion of the vaccination regimen.

This total exposure safety database would be supplemented by an adequately size control group, ideally one that has received a placebo control, as

well as available safety data from clinical trials in post-authorization or post-licensure use in adults.

In the event that older adolescents, those 16 to less than 18 years of age, had been included in an adult efficacy trial, we would consider inclusion of that older adolescent age group in an original licensure application previous in adults, with subsequent consideration of licensure for use in the younger adolescent age group based on immunobridging and safety data.

An emergency use authorization of a COVID-19 vaccine for use in adolescents, similar to licensure, will require evidence of effectiveness. And for this we would also expect this evidence of effectiveness to come from an adequately powered immunobridging trial with descriptive clinical endpoint efficacy data as available. We would expect the same size clinical trial safety database as for licensure, although, with a somewhat shorter overall duration of follow up, in order to address the emergency situation.

We have considered that a median follow up two

months, after completion of the vaccination regimen, would be sufficient to support emergency use authorization of a COVID-19 preventive vaccine in adolescents provided that there are no safety issues that would warrant a longer period of follow up.

This consideration accounts for physiologic similarity between adolescents and younger adult age groups, similarity in COVID-19 disease incidents between adolescents and younger adult age groups. And also takes into consideration that there would be safety data available in many thousands of adults, specifically many thousands of younger adults that would help to inform risk in adolescents.

This approach is reflected by FDA's May 2021 extension of emergency use authorization for use of the Pfizer-BioNTech COVID vaccine in adolescents 12 to less than 16 years of age. Also reflected by the precedent with the Pfizer-BioNTech vaccine, FDA would consider including the older adolescent age group, those 16 to less than 18 years of age, in an emergency use authorization for use in adults, if older adolescents

in this age group had been included in the adult efficacy trial.

Turning now to data considerations for younger age groups, again, we would expect that licensure of a COVID-19 preventive vaccine for use in younger pediatric age groups could be supported by evidence of effectiveness from an immunobridging trial, one that is adequately powered, and also includes descriptive clinical endpoint efficacy data as available.

Following the typical age de-escalation approach in pediatric development, we would expect multiple immunobridging trials each independently powdered for the age group involved. The examples that we gives in this presentation, and in our discussion questions, are six to less than 12 years, two to less than six years, and six months to less than two years.

There's nothing magical about these age cutoffs. They merely reflect generally what FDA has discussed with individual vaccine manufacturers in terms of their approach to pediatric development and age de-escalation. And there are slight differences

across the various pediatric development programs for COVID-19 vaccines that are currently underway.

We would expect for each of these age groups, no matter what the exact age cutoff is, a safety database of at least a thousand vaccine recipients, vaccinated with the age-appropriate dosing regimen intended for licensure, and with a median follow up of at least six months after completion of the vaccination series. Plus, as was the case with adolescents, and also for that matter with adults, an adequately sized control group, ideally receiving a placebo control, as well as consideration of all available safety data of clinical trial experience, and experience with post-authorization or post-licensure use in older age groups, those being adolescents and adults.

Consideration of emergency use authorization, of COVID-19 vaccines for use in these younger pediatric age groups, we believe is more complex. In consideration of whether to consider in the first place extending an emergency use authorization of a COVID-19 vaccine for use (audio skips) age group, would include

trajectory of COVID-19 epidemiology in the U.S., a burden of COVID-19 disease in these younger age groups, and therefore, the anticipated benefits of making the vaccine available. And finally, the robustness of available safety data, including from clinical trials in the specific age groups as well as experience in old age groups, to inform risk assessment.

Because of all of these considerations, and age groups specific differences, a conclusion of clear and compelling safety and effectiveness to support emergency use authorization, and, indeed, the need for emergency use authorization, may be less certain for younger pediatric age groups than for adolescents and adults. This is one of the questions on which we would like to receive input from the VRBPAC today.

If it were determined that there were a need for emergency use authorization of a COVID-19 vaccine for use in younger pediatric age groups, data that could potentially support such an emergency use authorization, in an age group specific manner, would include, first, evidence of vaccine effectiveness from

an adequately powered immunobridging trial, plus descriptive clinical endpoint efficacy data as available, and would also include the same size clinical trial safety database, as that which would support licensure, with a sufficient duration of follow up to assess risk.

What would be a sufficient duration of follow up? Well, you'll notice that we did not make a proposal here on the slide. And this is another question that we would like the VRBPAC to discuss and provide input on today. Considerations for sufficient duration of follow up, to potentially support emergency use authorization in these younger age groups, would need to consider the anticipated benefits in these age groups, and in an age group specific (inaudible) manner would need to consider available safety data from clinical trials in post-licensure or post-authorization experience in older age groups, and would also need to consider physiologic differences between younger pediatric age groups versus older age groups and adults. We recognize that these are very complicated

considerations and we look forward to the discussions this afternoon.

To remind you of the discussion items, first of all we would like the VRBPAC to discuss that in the situation where provided there is sufficient evidence of effectiveness to support benefit of a COVID-19 preventive vaccine for pediatric age groups, please discuss the safety data, including database size and duration of follow-up, that would support, first of all, emergency use authorization, and second of all, licensure. We would like the discussion to consider age group specific factors.

Secondly, in the situation where there is sufficient evidence of effectiveness to support benefit of a COVID-19 preventive vaccine for adolescents 12 to less than 18 years of age, we would like the committee to discuss the safety data, including the database size and duration of follow up, that would support licensure.

And finally, we would like the committee to discuss studies following licensure, and/or issuance of

an emergency use authorization, to further evaluate safety and effectiveness of COVID-19 vaccines in different pediatric age groups.

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

ADDITIONAL Q & A SESSION

DR. MONTO: Thank you so much, Dr. Fink. As usual a very clear presentation of topics in which there are not so clear answers. We have about 10 minutes for questions right now. And then we're going to again ask you to please stay with us this afternoon, as I know you will, because I'm sure there will be questions that come up. During our discussion we're not going to have the time to really be able to answer everybody's questions, which starts with Dr. Kurilla.

DR. KURILLA: Thank you. Great presentation, Doran. The question I have is I'm struggling a little bit with the immunobridging. You made the point that we don't always necessarily have to know the correlate

(inaudible) of protection and then in this case we don't know the correlate of protection. But, I'm a little concerned with the fact that we're talking about a vaccine that was derived from a viral sequencing that is now well over a year and a half old. And that sequencing -- that strain is actually not circulating any more. And so when you're trying to immunobridge immune responses against the vaccine, to clinical benefit, you're looking at clinical benefit -- clinical efficacy that was derived from a different set of circulating strains.

And so I'm having a little trouble as to how we can actually estimate the likelihood of ongoing protection from what is now a new set of circulating strains going forward.

DR. FINK: Thank you. You know, that is a very important question, not only for pediatric age groups, but also for adult age groups who have already been vaccinated.

DR. KURILLA: Sure.

DR. FINK: And, so, as we discussed back in

October, and at the various VRBPAC meetings for consideration of specific EUA requests, continuing evaluation of vaccine effectiveness in the post-authorization, and even post-licensure period, as new strains and variants merge (inaudible) will be of utmost importance.

And so, if data, at the time of a consideration of a pediatric vaccine licensure or emergency use authorization, suggested that the currently available vaccines, based on that original strain, were no longer effective against the variant currently in circulation, then we would need to take those data into account. And we may decide if there is strong evidence that currently circulating strains are not adequately covered by the vaccine, we may decide that the immunobridging approach, as described in my presentation, would not be sufficient.

Based on currently available data, I think we are still seeing very good levels of protection. And so, against the variants that are currently circulating. And so, for that reason we are going with

the approach as described in my presentation, and in the briefing document.

DR. KURILLA: And is that made clear in you guidance to manufacturers that it's not just what their phase three results showed, but rather an ongoing evaluation?

DR. FINK: I think we've been clear in our discussions with vaccine manufacturers.

DR. KURILLA: Okay, thank you.

DR. MONTO: All right, and, just in general, I think that we should try to keep our discussion away from the variant issue because it's a global issue; it's not related only to some of the pediatric questions, which are complex enough. Dr. Cohn?

DR. COHN: Thanks, Dr. Fink, that was great. One clarifying question before the discussion this afternoon, is FDA focused on those age groups as the only age groups in terms of the breakout, or would FDA consider different breakout, especially between that age two and six where potentially there could be some changes in terms of school-age children versus

preschool age children?

DR. FINK: As I mentioned in my presentation, the specific delineation of age groups that were presented in my briefing documents -- or in our briefing documents, and in the slide, are roughly following the approach to pediatric development and age de-escalation that has been proposed and discussed with individual vaccine manufacturers. If there were scientifically compelling arguments to consider subgroups within those age groups, or to consider different age cutoffs, we would consider those arguments.

What I presented really reflects a breakdown in terms of the timing upon which we expect data to become available for various age groups.

DR. COHN: Thank you.

DR. MONTO: Thank you. Dr. Nelson.

DR. NELSON: Good morning. Thank you, Dr. Fink that was an outstanding presentation. Very well thought out and a thoughtful approach to the immunobridging approach, which clearly clinical

efficacy endpoints exclusively are likely infeasible at this point. So it did set the stage for our discussion this afternoon.

I'll avoid the variant question, although I do share some of the same concerns that Dr. Kurilla had, as we move forward with respect to efficacy. But since this meeting is focused on safety, I wondered if you'd clarify for me a couple of things. One was on Slide 7 you talked about features of scientifically rigorous pediatric immunobridging trials. And you talked about the comparator group, and that the data needed to be -- or the demographics of the groups, so the active group and the younger age group being study, needed to be similar to the comparator group, presumably the older age group, older adolescents, and young adults.

But you made specific mention to similar demographic variables, which I would assume include ethnicity and other things. So in recognition that those adolescent and young adult trials did not sufficiently enroll in some cases specific ethnic groups, how do you reconcile the approach, or how data

will be presented for analysis in immunobridging settings, as question number one?

The second one is -- oh, well, let's start there.

DR. FINK: Okay. Well, we expect and encourage (inaudible) vaccine manufacturers to do whatever they can to ensure adequate representation of racial and ethnic minorities in their clinical trials. We understand that sometimes clinical trials do fall short of the goals. And, in this case, those shortcomings are reflected in the labeling of the vaccine, and factsheets in the case of emergency use authorization and in the package inserts in the case of licensed vaccines.

DR. NELSON: That's fair and very helpful. And, the second one was a little bit unrelated, but it talks about the EUA standpoint. And when we're talking about small signals, particularly in this population relatively smaller trials than the 40,000 plus that we saw with the adult trial leading to the initial EUA authorization. My question is, will small signals

generate a pause for a vaccine specifically, or will they extend across all relevant vaccine?

And I know that may be hard to predict without understanding the exact signal or scenario, but I wondered if you'd give us what the approach might be as we go through our risk/benefit discussion this afternoon. Thank you.

DR. FINK: So that is a hypothetical question, you're right; it's very difficult to answer in the abstract. If we were to encounter a signal in the post-authorization, or post-license -- well, if we were to encounter a signal in the post-authorization use of a vaccine -- let's keep it to that for now -- that, we felt, warranted a pause. We would consider very carefully whether that signal applied only to a specific vaccine, or to a subclass of COVID-19 vaccines, or to COVID-19 vaccines in general. And we would have to follow the available data to make that determination.

DR. NELSON: Thank you.

DR. MONTO: Thank you, one final question from

Dr. Kim. Dr. Kim, please.

DR. KIM: That was great, Dr. Fink. I have a question regarding immunobridging. In your discussion you mentioned that basically the reference group will be the 18 to 25 year olds for the younger age adolescents and children to be studied. Given -- don't we have data on 12 to 17 year olds at this point in time so that we can narrow the age range of the comparison group (inaudible) basically one group (inaudible) immunobridging to 12 to 17 year olds compared to children that are being considered -- those that are younger than 12 year olds? So immunobridging would utilize the data from 18 -- not from 18 to 25 year olds, but 12 to 17 year olds. Is it possible?

DR. FINK: So thank you for that question. That is a question we have considered and discussed. And, there are benefits and risks to that kind of an approach. Though, in terms of potential benefits where you described is that the adolescent age group would be closer in age and presumably closer in terms of the mechanisms of vaccine elicited immunity and immune

response to the younger pediatric age groups. And so, potentially would be a comparison -- a reference group that is less prone to bias than using a younger adult group.

On the other hand, effectiveness of the vaccine in the adolescent group, if inferred from immunobridging to the original adult reference group, would be based on a statistical comparison. And so then, if you were to use the adolescent group as the reference group for a younger pediatric age group that would be a statistical comparison to a statistical comparison. And you therefore introduce the risk of bio-creep where you're working with a non-inferiority margin that allows for a potentially larger and larger difference in immune response to be successful in (inaudible) the statistical hypothesis testing.

So, because of this risk, we would consider that situation to lend itself most appropriately to maintaining the younger adult population as the reference group for all pediatric age groups. And, we have used this approach for other FDA licensed vaccine

approved for use in pediatric populations.

DR. KIM: Great, thanks for the explanation.

INDUSTRY PERSPECTIVE: CONSIDERATIONS FOR COVID-19 VACCINE PEDIATRIC TRIALS

DR. MONTO: Okay, thank you. And thank you, Dr. Fink, once again. Final talk before lunch, an Industry Perspective: Considerations for COVID-19 Vaccine Pediatric Trials, from Phyllis Arthur. Ms. Arthur.

MS. ARTHUR: Thank you so much for inviting us to give a quick presentation of this, the very important topic for industry. My name is Phyllis Arthur. I'm the Vice President for Infectious Diseases and Emerging Science Policy at BIO. BIO is a trade association here in the United States that works with biotech companies working in human health, food and agriculture, and industrial application of biotechnology. Our members, actually as you know, responded across COVID-19 issues, therapeutic and of

course vaccine, as well as diagnostic. And we're very interested in this particular topic.

Mainly we wanted to support and underscore the rigor of the FDA's approach to this issue of pediatric trials for the COVID-19 vaccine. And at the end of my presentation I'll highlight just a few questions that we have for the agency that we'd like to have addressed for the sponsors as they work closely with the FDA to execute their pediatric trials.

So, I think that there's a lot of agreement that there's a need for understanding of how the COVID-19 vaccines will work in pediatric populations. And the sponsors support the approach and the recognition of the way the FDA is approaching this particular issue.

Children, as we've heard from the presentations today, generally have had less burden of disease from COVID-19 infection than adults throughout this pandemic. But, there have been some very important data showing that children are still impacted both with hospitalization and severe disease.

On June 4th, the CDC presented at their (inaudible) team meeting some updated data on COVID-19 disease in adolescents. And there were over 200 (inaudible) adolescent hospitalizations that required intensive care, and five percent of those actually required invasive mechanical ventilation. Additionally, this data showed that the rate of adolescent hospitalization have been rising over the last two months of the pandemic, going from .6 per hundred thousand in March, to 1.6 per hundred thousand in April.

Accumulatively, COVID-19 associated hospitalization rates, from October of 2020 to April of this year, were 2.4 to three times higher than we seen in a normal influenza season with (inaudible) proceeded hospitalization rates. And so I think it's important for us to think about both the impact on the adolescents and children themselves, as well as of course the important issue that was discussed earlier about the impact of adolescence in the overall response to the pandemic.

Obviously we've heard as well today about this new syndrome that's been associated with COVID-19 infections, the MIS-C. And we think that that's an important severe impact that it can have on the heart, lung, kidney, brain, skin, eyes, and gastrointestinal (inaudible) organs. How do we take into account in terms of how children and adolescents are impacted by COVID-19 infection?

As we discussed earlier, vaccination is increasing among adults and young adults. And that's very important to reaching overall protection and reduction, or limit and ending of the pandemic.

Strategies focused on immunization of these particular populations are certainly important, but you want to make sure that we don't just focus on young adults and older adults if we're going to actually end the pandemic and achieve herd immunity. Children will be a key part of that exercise.

For pediatric vaccine clinical trials, sponsors have had decades of experience in working with the FDA on how to approach these trials. And I think

Dr. Fink covered many of the examples that we were thinking about as well, particularly how efficacy of HPV vaccines was the immunobridge into efficacy and safety for younger populations, as a good example.

We'd also hold up the example of influenza, where it's a good comparator to what we may see with coronavirus as we move from pandemic period to endemic period, where there's a need to understand year-on-year epidemiology and then the (inaudible) and how we may have to look at multi-year studies as a way to really capture overall efficacy in younger population. So, we think there are several different ways to look at trials moving forward, and how to get to younger age groups and look at efficacy over the long term.

Sponsors are obviously very pleased with the various options and approaches that really maintain the high standard of how we do research in the COVID -- in pediatric populations. And (inaudible) support the various approaches laid out by Dr. Fink, including randomized controlled trials that are the gold standard for clinical trials, age de-escalation, immunobridging,

and of course dose-ranging. And then, of course, rigorous safety monitoring both during the trial period and in the post-trial period, and as well as continuing in the post-marketing period.

So we had a few questions that we wanted to share with the FDA and the panel for consideration. Can the agency comment on the regulatory pathway for authorization of lower pediatric doses compared to the doses that are authorized currently in adults? Would immunobridging support use of lower doses in pediatrics?

What are the FDA's plans for vaccine effectiveness studies in the pediatric population? What are the expectations for sponsors with regard to vaccine effectiveness studies moving forward? And how will FDA and sponsors collaborate on vaccine effectiveness studies?

I'll add an additional question here even though it brings up a topic we just were discussing, which is how is the FDA viewing or approaching pediatric study requirements when it comes to variants.

So I know we just discussed we weren't going to talk about variants, but it's one of the questions we have as well as industry. Would FDA be in favor of immunobridging (inaudible) in infants, or would separate studies of pediatric populations for variants of concern, be required.

How should sponsors approach co-administration studies -- this has been discussed today as well -- and concomitant use of these vaccines as we move into the more complicated schedule of pediatric immunization?

How will FDA use data from pediatric population from the safety monitoring systems that are currently used for COVID-19, for example, V-Safe?

How does the FDA intend to collaborate with other regulators outside of the U.S. to ensure global alignment on the approach to vaccine pediatric programs?

And how will the FDA's approach evolve as COVID-19 moves from the pandemic phase right now to an endemic phase where the vaccine may be given more routinely in some approach?

So these are our questions, and we're very pleased to have the opportunity to speak to the committee today and participate in these important discussions. Thank you, very much.

DR. MONTO: And thank you so much. You've asked a whole lot of very important questions, which really are directed both to FDA and to our group. We have a few minutes, any of the voting members got comments -- or Dr. Gruber, would you help us out?

DR. GRUBER: Yes, thank you very much, Phyllis. You make a couple of important questions and I think that some of them we will be certainly addressing when we talk with the particular vaccine manufacturers in our discussions and collaborations on pediatric trials and pediatric development of COVID vaccines. I don't think that we should really engage in these types of discussions today, and really focus on the discussion points and questions that the FDA has formulated.

One quick response in terms of global alignment with other regulators, we of course have

frequent collaborations and exchange with our regulatory counter-parts to make sure that the approaches that they're using regarding development of COVID vaccine in the pediatric populations, how we're looking at variants of concerns, that we really try to align our approach there.

Again, thank you, this is really food for thought and I trust that your questions are going to be discussed and answered in the different (inaudible) available to us. Thank you.

DR. MONTO: And thank you, Dr. Gruber, for getting us off the hook in terms of answering questions that we're not in the position to answer. So now we have come to almost noon. I see no hands raised from the committee, so I think we're going to take a half hour break for lunch and reconvene for the open public hearing at 12:30 eastern. 12:30 eastern for the open public hearing.

[BREAK FOR LUNCH]

OPEN PUBLIC HEARING

MR. MIKE KAWCYNSKI: All right. Welcome back and, Dr. Monto, take it away.

DR. ARNOLD MONTO: Well, welcome back for the open public hearing. I'd like to welcome you all. Please note -- so welcome to the open public hearing. Please note that both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency, the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the Committee of any financial relationship that you may have with the product -- the sponsor, its produce, and, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of expenses in connection

with your participation in this meeting. Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. So over to you, Prabha.

DR. PRABHA ATREYA: Good afternoon, everyone. Thank you. Welcome to the open public hearing. We have a few speakers who pre-registered, and each have five minutes to speak. We will start with Dr. Sydney Wolfe. Dr. Wolfe, can you start?

DR. SYDNEY WOLFE: Sydney Wolfe, Public Citizen's Health Research Group. I have no conflict of interest. Last week in the morbidity/mortality weekly reports of the CDC, the following statement was issued relevant to the 12 to 17 year olds that the current issue of EUAs has to do with. "Recent increases in COVID-19 associated hospitalization rates and the potential for severe disease requiring intensive care unit admission, invasive mechanical ventilation among

adolescents indicated an urgent need for vaccination in combination with correct and consistent mask wearing by persons not yet fully vaccinated."

The data, which includes 14 states, looked at for hospitalizations between January 1st of this year and March 31st included, as I said, 240 hospitalizations. Almost a third, 64, required intensive care unit admissions. 10 required mechanical ventilations. Fortunately, none of them died.

These are obviously people who were not vaccinated at all in this 12 to 17 year old age group. And the message at the CDC said -- urgent need for vaccination in such people. The next slide comes from little is there in the public eye from Moderna's statement on May 25th. Out of roughly 1,000 placebo recipients in their trial of 12 to 17 year olds, four out of 1,000 got COVID. Whereas, out of 2,000 slightly more confirmed cases in the vaccine group there were none -- so no confirmed cases. And as they say, this is a 100 percent calculated efficacy.

We go back to these data just to get on this

issue of the need in people 12 to 17 -- obviously, older the same and younger, but those have not been tested yet -- for vaccination. So without vaccination, hospitalizations -- just, again, 14 states -- intensive care unit admissions and so forth. And this segues into one of the briefing document pages, page 12, "Why Use Placebos in Future COVID-19 Randomized Trials?" is the question being asked.

"If another COVID-19 vaccine is licensed or authorized for use in the age groups enrolled in the trial recommended by public health authorities and widely available, such that it is unethical to use a placebo control, the licensed or authorized COVID-19 vaccine could serve as a control." So this is talking about planning future trials. Obviously, the Moderna and/or Pfizer trials were or could have been organized that way. But as we get into other trials in that age group and younger age groups, I fully agree with this idea.

And it certainly brings to mind the issue that I've raised -- and I think others did -- in the first

Pfizer meeting, which is what happens in the case of the Pfizer -- the 2,000 people who were in the placebo group? And I had advocated they should be immediately notified and offered a vaccine, and I think that that's been done. I believe it's been done for the Moderna.

And I raised the question -- which I hope the answer's yes -- has it been done for the 2,000 children -- the 1,000 children in the Moderna and roughly the same amount in the Pfizer age 12 to 17 who got a placebo? They should get a vaccine. Just as in future trials nobody should be getting a placebo in a trial.

The reasons for having these comparative studies, obviously, is an ethical reason. It would be unethical once there's an authorized vaccine for that age group. Parents would be much more willing to enroll their children since they would always get some treatment, not a placebo.

And related to that obviously, clinical trials for subsequent vaccines for that age group would therefore have less difficulty with enrollment, with one already authorized vaccine around for whichever age

group. The next one is below 12. It would be difficult to enroll people if you are telling them you have a 50 percent or a 30 percent chance of getting a placebo.

And finally, this has to do with Question 3 that you're being asked to address today. "Please discuss studies following licensure and/or issuance of an EUA to further evaluate safety and effectiveness of COVID-19 vaccines for different pediatric age groups." Since FDA has not yet authorized publicly -- at least, we don't know it's been done, and it's supposed to happen in the next few days -- the Moderna vaccine for 12 to 17 year old adolescents, why were these data not provided during this meeting. As you know, there was not a comparable meeting before the Pfizer 12-17 was authorized, and so there wasn't an opportunity to do it. But it should be part of the discussion.

And in conclusion, a much more evidence based discussion of Question 3 -- which I just read -- could have thereby occurred. Further evaluation of any vaccine for any age groups needs to be predicated on

what is already known. Thank you very much.

DR. PRABHA ATREYA: Thank you, Dr. Wolfe. The next speaker is Dr. Peter Doshi. Let us know if you need us to move the slide, please.

DR. PETER DOSHI: Hello, I'm Peter Doshi. Thanks for the opportunity to speak. If you could please advance to my title slide showing my financial disclosures. For identification purposes, I'm on the faculty at the University of Maryland and an editor at the *BMJ*. And I have no relevant conflicts of interest. Next slide, please, the slide labeled "Slide A" at the top right.

So the question is what is the evidence in children thus far? Let's take Pfizer's trial of 12 to 15 year olds, which supported the recent EUA. In this trial, harms outweighed the benefits. The placebo group was better off than the vaccine group. I know that's a blunt way to put it, but the reason is because efficacy benefits were rare. Whereas side effects were common.

I'll explain that. In terms of the benefits,

the reported 100 percent efficacy was based on 16 COVID cases in the placebo group versus none in the fully vaccinated group, but there were around 1,000 placebo recipients. So just 2 percent got COVID. Put another way, 2 percent of the fully vaccinated avoided COVID, whereas 98 percent of the vaccinated wouldn't have gotten COVID anyway.

But on the other side of the ledger, side effects were common. It's on my slide. Three in four kids had fatigue and headaches. Around half had chills and muscle pain. Around one in four to five had fever and joint pain. The list goes on.

In sum, all fully vaccinated 12 to 15 year olds avoided symptomatic COVID, but most wouldn't have gotten COVID even without the vaccine. So the benefit is small, but it came at the price of very common side effects that were mild to moderate in severity and lasted a few days. And then, there are the long term effects about which we still know nothing. I'll come back to this point. Next slide, "Slide B," please.

Why do so few vaccinated children enjoy any

efficacy benefit? As I said, one reason is that few kids got COVID, at least during Pfizer's trial. Also, many infections are asymptomatic. But another reason is that many children are post-COVID at this point.

The CDC estimate from 25 million children were infected by March. That translates into 23 percent of kids zero to four years old and 42 percent of children five to 17 years as being post-COVID. And I say post-COVID because the evidence to date suggests that the immune response following natural infection is robust and long lasting. I think this is why so few vaccinated kids reap any benefit. Next slide, "Slide C," please.

Now, let's talk about long term harms. There's a view out there that serious side effects always occur within six weeks of dosing. Well, it's just not so simple. The fact is that, historically, side effects were not always discovered so quickly. For pandemics and influenza vaccine, cases of narcolepsy in adolescents were first reported around nine months after vaccines were given. And now, with

COVID vaccines, it wasn't until this month, four or five months into the vaccination campaign in Israel, that myocarditis was recognized as a harm in young men.

So it's not simply a matter of how long after dosing did these adverse events occur. The crucial question is when are these adverse events noticed, researched, and established as linked to the vaccines. The pharmacovigilance timeline matters.

Unless you recognize harms soon after they occur, you can't use that knowledge to prevent harm in the next person about to get the vaccine. And on long term harms, we know nothing. All we can do is theorize, say, by considering the mechanism of action, vaccine biodistribution and other essential studies that we outlined in our June 1st citizen petition. Next slide, "Slide D," as in David, please.

Next, I want to address this idea of vaccinating children to protect adults. I encourage the Advisory Committee to read Dr. Lavine et al's editorial to explain why, "Vaccinating children is likely to be of marginal benefit in reducing the risk

to others." And even if you think a small benefit is better than nothing, let's not forget that it's an unproven hypothetical benefit. We need confirmatory evidence, not just assumptions.

And then there's the ethics and the law. FDA can only indicate a product for use in a given population if benefits outweigh risks in that same population. So if benefits don't outweigh risks in children themselves, it can't be indicated for children, full stop. Whether vaccinating children might help adults is a moot point. Final slide, "Slide E," please.

In summary, we must avoid a fiasco. EUA criteria are not met because there is no emergency for children. Thus far, risks outweigh benefits, and we know nothing about long term safety other than history's lessons to be very cautious. Does this mean we should prevent parents desiring to vaccinate their children? No.

Access does not require an EUA or BLA. Rather, an expanded access program can thread the

needle, providing access to vaccines while being honest about the evidence that it has not been demonstrated that benefits outweigh risks. FDA approval must represent a high bar of robust evidence. Otherwise, the whole point of regulation is lost. Thank you for listening.

DR. PRABHA ATREYA: Thank you, Dr. Doshi. The next few speakers do not have any PowerPoint presentations. The next one is Dr. Jacqueline Miller.

DR. JACQUELINE MILLER: Thank you and good afternoon. My name is Jacqueline Miller, and I'm the head of development for infectious diseases at Moderna. As a pediatrician and mother, I am very encouraged that the VRBPAC has convened to discuss authorization and licensure criteria for COVID-19 vaccines in the pediatric population.

This pandemic has dramatically altered life for all Americans over the past year, including our children. Because of concerns of COVID-19 disease and transmission, children have had to adapt to distance learning, reduced group activities, and the restricted

ability to interact with other children and their teachers. School closures have significantly impacted the lives of students. Education is one of the strongest predictors of an individual's future success, and the impact of longer term school closures on the future health and achievement of children have not yet been quantified.

According to the CDC, 18 percent of COVID-19 cases reported during the month of April occurred in children and adolescents. To date, more than 3 million cases of COVID-19 have occurred in children. And while children are less frequently impacted by the severe complicates of COVID-19, we have observed unusual and severe disease in children, including MIS-C which is characterized by high fever, severe systemic inflammation, and hospitalization. As with adults, children of color have been disproportionately impacted by this complication with 64 percent of cases occurring in Black or Hispanic children.

Moderna strongly supports the vaccination of children and is actively generating clinical data. We

recently communicated the topline results of our Teen COVE study, which enrolled more than 3,700 children 12 to 17 years of age, 26 percent of whom were from communities of color. The vaccine efficacy in the nearly 2,500 adolescents who received Moderna COVID-19 vaccine was observed to be 100 percent when using the same case definition as in the pivotal trial for adults. When using a less restricted case definition, the vaccine efficacy was 93 percent, and asymptomatic infection occurring 14 days after the first dose was reduced by 60 percent.

The primary immunogenicity endpoint of the study was met, demonstrating that the antibody responses induced by the vaccine in 12 to 17 year old adolescents are similar to those in adults 18 to 25 years of age. The safety profile of the vaccine was generally similar between adolescents and young adults. We will continue to monitor these study participants for efficacy, immunogenicity, and safety endpoints for 12 months after vaccination. And we submitted our application for the authorization of emergency use to

the U.S. FDA yesterday.

We're also conducting Kid COVE, a clinical trial in pediatric subjects in over 6,700 children who are six months to 11 years of age. We have focused on ensuring the safety of children and, therefore, are conducting a dose ranging study to see if a lower dose might be effective in younger children. We look forward to providing additional update to this study as information becomes available.

The available data in children complements the data we are continuing to accrue in the pivotal Phase 3 study and through rigorous safety monitoring through the emergency use authorization program in collaboration with the FDA and CDC. Over 100 million Americans have received at least one dose of COVID-19 vaccine, and the benefit-risk profile remains strongly favorable.

We remain committed to comprehensive, ongoing safety monitoring, signal detection, and proactive and transparent risk communication in collaboration with the FDA, CDC, and other regulatory agencies.

Vaccination against COVID-19 will not only directly benefit children's health but also enable them to safely return to school and other activities. We are extremely grateful to the VRBPAC and the FDA for meeting today to provide guidance about the data necessary to support emergency use authorization and licensure of COVID-19 vaccines in children. Thank you.

DR. PRABHA ATREYA: Thank you, Dr. Miller. The next registered speaker is Ms. Kim Witczak.

MS. KIM WITCZAK: Great. Good afternoon. My name is Kim Witczak, and I'm speaking on behalf of Woody Matters, a drug safety organization started after the death of my husband due to an undisclosed side effect of antidepressants. We represent the voice of families who live every day with the consequences of the current drug safety system. I'm also on the board for USA Patient Network, an independent patient voice advocating for safe and effective successful medical treatments.

There are over 74 million children between zero and 17 in the United States and close to 2 billion

globally. While I don't have kids personally, I care deeply about them. They are our future, and they will be here after you and I leave this world. And that's why I'm here today.

I have great concerns over the authorization or, worse yet, fear a premature full approval of COVID vaccines for children. For starters, is there really an emergency with children and COVID? The data shows kids are neither in danger nor dangerous. They are a small percent of the total cases with even a smaller number who experience serious illness or die. I question the timing of last Friday's CDC announcement of the rise in children being hospitalized with COVID. The media ran with it, and more fear was stirred, perfectly timed in advance of this meeting.

Does the public truly understand how pediatric trials work, like, how few children are actually in them, how efficacy protection is often determined by immuno-bridging based on an assumption using adults' experience, or safety is considered adequately characterized using only several hundred trial

participants? Assumption on top of assumption. This hardly makes me feel confident in the one size fits all shots -- on how they're being evaluated, especially when there's a potential to be used on millions of children. Trust me, the average person doesn't understand this. All they are being told is it's safe and effective.

The truth is we don't really know that much about these vaccines. The safe and effective messaging is being thrown around from everyone from government officials, the media community, religious leaders, to Hollywood celebrities. Then, you add in all the promotions, like multimillion dollar lotteries, free donuts, free shots at the local bar, and so on. This subconsciously creates the allusion that there are no downsides whatsoever, nothing to weigh or consider.

Right now, the discussions around vaccines seems to be less and less about the science and becoming more and more driven by political agendas and motivations. With all the talks of mandates and having kids vaccinated by fall, there is certainly political

pressure to approve and license these vaccines. However, this is completely outside the FDA's purview and opens a Pandora's box for compulsion.

Like mandates, approving vaccines to bolster public confidence and convert the vaccine-hesitant is backwards and, again, is outside of the FDA's legal purview. Last week, I, along with a group of 26 researchers and clinicians from around the world, filed a citizen petition. I believe you should have a copy in your documents today. We outline several efficacy and safety measures that must be met before you consider granting full approval, and that includes: completing at least two year follow up in participants in pivotal clinical trials, even if they were unblinded and we lost the placebo control group; ensuring the evidence of effectiveness outweighs the harm in special populations, including babies, children, and adolescents; and a thorough investigation of all adverse reactions, including deaths. We simply cannot ignore the growing evidence of harm and just accept the narrative "It's a good thing. That means the shot is

working."

This reminds me of the same attitude the medical establishment had when we were trying to get black box suicide warnings added to anti-depressants. And suicide was dismissed as inherent in the disease of depression. We need to dig deeper and find out if there's causal link, like Norway's government did with the 100 nursing home deaths. And they found that 10 were likely and possibly 26 were causal. What has the U.S. done?

As you are debating the merits, please look inward and ask yourself if this is truly the right thing for humanity. What if years down the road you found out the decision you made today negatively impacted your children and grandchildren's health? Do you want this on your watch? I often think back to the 1991 FDA Advisory Committee meeting debating the link between Prozac and suicide and violence. At the time, every one of the Advisory members with financial ties to industry voted no. It wasn't until 2004, 13 years later with more antidepressants on the market and now

approved for kids, that black box warnings were eventually added. How many lives were destroyed, including my husband's, because of that decision made in 1991?

My closing message to you is this: go slow. There's no rush. The future generations are depending on you. Thank you.

DR. PRABHA ATREYA: Thank you, Ms. Witczak. The next registered speaker is Ms. Terri Diaz.

MS. TERRI DIAZ: Hi. My name is Terri Diaz, and I am co-founder of GPAC, Global Patient Advocacy Coalition. I have no financial interests. I'm a patient who was harmed by an FDA approved medical device, and I am a passionate advocate for all patients to have proper informed consent. Thank you for having me speak today to speak about the use of COVID vaccines in children.

According to the CDC website, although children can be infected with COVID-19, can get sick, and can spread the virus to others, less than 10 percent of COVID-19 cases in the United States have

been among children and adolescents aged five to 17 years. Compared with adults, children and adolescents who have COVID-19 are more commonly asymptomatic or have mild, nonspecific symptoms. Children and adolescents are less susceptible to infections and have milder cases.

For a population that has the absolute lowest risk, I feel that it is imperative to look at the current facts and emerging data for this disease and the mRNA vaccines. There are many unknowns that the scientific and medical communities are still working on to understand. Our children are a vulnerable age group, with many years of growth ahead of them. And I urge you to use extreme caution when making decisions about the youth of this experimental mRNA vaccine.

Please consider first and foremost the fact that we do not have long term safety data. It is dangerous and reckless to expose children to an unnecessary procedure where we do not know the long term outcome. There are many risks and complications that are emerging as more people have become

vaccinated.

Last month, a CDC advisory group recommended an investigation into further study of the possibility of a link between myocarditis and the mRNA vaccine, which includes those from Pfizer and Moderna. In a May 24th meeting, the CDC advisory group said the data from the VAERS reporting system showed a higher than expected number of observed myocarditis or pericarditis in ages 16 to 24 years old. In addition, a specially appointed epidemiological team in Israel has found a likelihood of a link between receiving the second dose of Pfizer's COVID-19 vaccine and the onset of myocarditis in young men.

As we know, Israel has been one of the first countries in the world to vaccinate the majority of its population. The resulting information that comes out may be beneficial in understanding how the vaccine affects the pediatric population. One June 1st, 2021, Israel's health ministry stated that it found the heart inflammation cases were likely linked to the vaccination. The study stated that there is a probable

link between receiving the second dose of the Pfizer vaccine and the appearance of myocarditis among men aged 16 to 30.

According to the findings, such a link was observed more among men aged 16 to 19 than any other age group. There is a possibility that our pediatric population could potentially have long term heart issues as a result of receiving the COVID vaccines. This could result in a lifetime of medical costs and a debilitating health complication. It would be most beneficial and in the best interest of our sons and daughters to wait until more scientific data is available before making any decision about administering the COVID vaccine to children and teens.

The lack of manufacturer accountability is something that should be highly considered. Currently, the FDA and the CDC reporting system is challenging at best, whereas most patients and even the medical community does not know how to report to VAERS, which means the number of adverse reaction reports are only a fraction of the actual reports. As of May 28th, there

were 294,801 of adverse event reports, and the manufacturer should be responsible for compensating patients who are harmed, disabled or who have died.

In the FDA briefing materials, it clearly states that the EUA can only be issued after certain requirements are met. One of those requirements is that there is no adequate approved and available alternative to the product for diagnosing, preventing, or treating the disease or condition. We have seen multiple studies come forward that have shown hydroxychloroquine and ivermectin as a successful treatment in fighting COVID-19.

This blatant and obvious fact complete discredits the need for an EUA. It is my recommendation at this time for the FDA to not approve or license any COVID vaccines until clinical trials have been completed and long term safety data is available. Long term safety data will give patients an opportunity to make informed decisions about getting a COVID vaccine. My mom, who was in a vulnerable population, received her full Pfizer vaccines in the

month of March, contracted COVID the end of April, and just passed away on May 14th, which makes me question the effectiveness of this vaccine.

In summary, as we do not have a full grasp on how the COVID vaccines are affecting people long term, I implore you to protect American children and refrain from making a decision until we have more scientific data. It is reckless and irresponsible for the FDA to approve these vaccines in children when we do not fully comprehend the long term affect. Thank you for your time today.

DR. PRABHA ATREYA: Thank you, Ms. Diaz. The next speaker is Dr. Ros Jones.

DR. ROS JONES: Hello, I'm a pediatrician from Britain from the Health Advocacy and Recovery Team, representing a group of British doctors and academics, and we have no conflict of interest. We're very concerned at the speed of rolling out COVID-19 vaccines to children while the safety data in young adults is still building. We all know that the risk of harm from COVID-19 infection reduces the younger the age group

under consideration, but it appears that for the side effects the opposite is true, with both thrombocytopenic complications and myocarditis both having higher prevalence in younger age groups.

And there clearly would have to be a tipping point where risk of harms exceeds potential risk of benefits. I would suggest that probably applies to young adults as well, but my concern here is as a pediatrician for children. We have no evidence that children need this, and we have plenty of evidence accruing that the risks of harm will outweigh any potential benefits.

Your VAER system is rather like our yellow cards, tends to have considerable under reporting and also problems with ascribing causation. But you have your near-live surveillance for health insurance, which seems especially useful. We've discussed that standard trials don't have sufficient statistical power to elicit rare and severe side effects. But there seems to be only one other alternative ever discussed, and that is simply, oh, just watching to post-marketing

surveillance.

And as everybody's said, that's under reported. It's delayed in coming through, and by the time you get this information, millions more children will have been vaccinated and potentially harmed. And one of the previous speakers was even questioning the ethics of using a placebo. And yet to my eyes, the question is about the ethics of vaccinating children that we don't know -- when we don't know this is safe.

So I just wonder if in the States -- we're watching this closely because in the UK it's just been authorized on a temporary basis, just as you have. But we haven't started using it, and we're desperately trying to prevent that happening. Would you have even considered at this time during the summer months when the risk of COVID is so low that you could randomize between states so you had some children who were going to get the vaccine now and others who would get it in a few months' time? You could have 100,000 or a million children in both arms of your study very quickly and really answer the safety data.

But at the moment, we're just rushing headlong into vaccinating children without adequate safety data, neither short term nor long time. And the ethics of that is quite, I think, horrific. And particularly as Peter Doshi said earlier on, if we start talking about herd immunity, the ethics of expecting children to take a risk of harm for the sake of older adults is totally unacceptable and inappropriate.

So like the last two speakers, I would plead with the FDA not to be rushing ahead with any further approval. But if you are doing so, then for goodness' sake at least consider delaying some of those so you get some decent data to help those of us in the rest of the world who are waiting with bated breath to see how this unfolds. Thank you.

DR. PRABHA ATREYA: Thank you, Dr. Jones. The next speaker is Dr. Meg Seymour.

DR. MEG SEYMOUR: Thank you for the opportunity to speak today on behalf of the National Center for Health Research. I am Dr. Meg Seymour, a senior fellow at the center. We analyze scientific

data to provide objective health information to patients, health professionals, and policy makers. We do not accept funding from drug or medical device companies, so I have no conflicts of interest.

We can all agree that it is of utmost (Inaudible) safety and effectiveness of vaccines for children across age groups. There must be an appropriate and favorable balance of the benefits and risks in order to support both an EUA and licensure. We agree with the FDA's assessment that the lower burden of disease in pediatric populations warrants more stringent criteria for safety and effectiveness than for adults.

In terms of the vaccine safety, we agree with the FDA in order to adequately assess risks in pre-licensure clinical trials, the safety database for each age group should be at least 1,000 vaccine recipients, plus control recipients. Given the millions of children who might be vaccinated using a licensed vaccine, we think it should be studied on a sample of at least 3,000 children. In addition, the FDA's

recommended follow up time of a median of at least six months at the completion of the vaccination regimen is not long enough. For an adequate assessment, FDA should require that children should be followed for a minimum of six to nine months, not a median that includes follow up of less than six to nine months.

Finally, we want to stress the importance of enrolling children from all racial and ethnic groups, including minorities who are most affected by COVID-19 in clinical trials of the vaccines. While we are happy to see that FDA encourages diversity in clinical trials, mere encouragement is not enough. Vaccines should not be granted EUA or licensure for use in populations for which they have not been tested and shown to be both safe and effective.

Please consider these points during your discussion today in order to ensure a favorable balance of benefits and risks for vaccines among the pediatric population. Thank you.

DR. PRABHA ATREYA: Thank you, Dr. Seymour. The next and final speaker is Ms. Nissa Shaffi.

MS. NISSA SHAFFI: Good afternoon. My name is Nissa Shaffi, and I'm representing the National Consumers league. I have no conflicts of interest. The National Consumers League was founded in 1899 by the renowned social reformer, Florence Kelley. General Secretary Kelley's support of vaccinations played a key part in mitigating a critical smallpox outbreak towards the end of the 19th Century. And her stalwart advocacy for immunizations has informed NCL's bedrock principles for vaccine education, confidence, and safety.

122 years later we are honored to persist in our pursuit to advance vaccines as vital public health interventions, and we extend our gratitude to the Vaccines and Related Biological Products Advisory Committee for the opportunity to present comment during this public hearing session. NCL appreciates that the FDA recognizing that emergency use authorization is not intended to replace the rigor of full approval and that randomized clinical trials are critically important for the definitive demonstration of safety and efficacy of a treatment. The diligent review and public engagement

that went into the EUA process for the COVID-19 vaccines currently available have helped our nation reach key milestones in immunization.

As our adult populations have benefited from these critical public health efforts, we are energized to extend that momentum towards our youngest citizens. Through our education and outreach of consumers, we support the FDA in its efforts to develop a safe and effective and expedited pathway towards a COVID-19 vaccine via EUA to help prevent the spread of the virus in pediatric populations. We are encouraged to learn of the Committee's approach towards evaluating the safety and efficacy of the COVID-19 vaccines, and we have great trust in the FDA's safety monitoring systems and call on the Agency to perform ongoing post-market surveillance to ensure the vaccines' continued safety and efficacy.

As we've observed with recent vaccine safety concerns, consumers rely on public health agencies to communicate and respond to any potential adverse events regarding the COVID-19 vaccine. We call on the FDA to

continue to sustain its robust interagency collaboration as we endeavor to vaccinate the nation. Although children are at lower risk of COVID-19 compared to adults and tend to experience milder symptoms, pediatric populations now account for 22 percent of new COVID-19 cases, compared to 3 percent last year.

As with adults, children and adolescents with underlying chronic health conditions are at higher risk for COVID-19 related hospitalization and death. The absence of a vaccine for pediatric populations will led to continuing transmission that will consistently put children at risk for infection. Furthermore, vaccine uptake for routine pediatric immunizations have declined dramatically during the pandemic.

It is essentially for public health officials, advocates, and parents to ensure that children are up to date with their vaccines and that children eligible for the COVID-19 vaccine receive their shot. Data shows that the COVID-19 vaccine currently available for children ages 12 to 15 is safe and effective and has

been recommended to be co-administered along with routine pediatric vaccinations. While COVID-19 has impacted the entire country, it has largely devastated communities of color.

Children of color, specifically Black and Hispanic youth, have been especially vulnerable. This has been even more apparent with the prevalence of multisystem inflammatory syndrome in children, a rare but serious COVID-19 associated condition that has been observed in children one to 14 years of age, 64 percent of which were reported to be Black or Hispanic.

To achieve meaningful herd immunity, we will need to ensure that children have access to a safe and effective COVID-19 vaccine and also consider the unique disparities that children of color experience in the face of the pandemic. Thank you to the Committee for your consideration of our views on this important public health issue.

DR. PRABHA ATREYA: Thank you, Ms. Shaffi. And this concludes the open public hearing for the public record, and so with the permission of the Chair,

I would like to announce a 10 minute break, the next item on the agenda. And then after 10 minute break, we will reconvene to start the Committee discussion this afternoon. Thank you.

[BREAK]

COMMITTEE DISCUSSION

MR. MICHAEL KAWCZYNSKI: All right. Welcome back to the FDA Center for Biologics Evaluation and Research VRBPAC meeting. We will now enter into the committee discussion. Dr. Monto, take it away.

DR. ARNOLD MONTO: Welcome back. Glad everybody is here a few minutes early. Our open public hearings were a little shorter than anticipated. So I'm delighted that we could start a few minutes early because we have a lot to discuss. And before we go on to some of the discussion topics, I wanted to make sure that everybody was comfortable with the presentations

we've had. I see Dr. Rubin has his hand raised. So I'll call on Dr. Rubin.

DR. ERIC RUBIN: Thanks, Dr. Monto. I have a question -- and it might be for Dr. Kirking if she's still here -- left over from this morning. It's true, as several people have pointed out, that the rate of COVID-19 is declining, but really that brings it down closer to -- it's still way ahead of many of the other viral diseases that we immunize children for. So I wonder if you can put COVID-19 in the context -- and the risk and benefits (audio skip) for children in the context of the MMR preventable disease, any of the other childhood vaccines that we use on a routine basis, just give an idea of the magnitude?

MR. MICHAEL KAWCZYNSKI: Dr. Kirking, there you go. Make sure you unmute. Go ahead.

DR. ARNOLD MONTO: Thank you for being there. Go ahead, please.

DR. HANNAH KIRKING: Yeah, I'm here. Thank you for the question. So just to clarify, make sure I'm understanding, you want to know how to put the

context of COVID-19 declining case rate without vaccination of children or in the context of what we see with measles, mumps, rubella first?

DR. ERIC RUBIN: Well, no, I guess I'm thinking about -- the question that we're faced with is something of a risk-benefit question. Is there enough disease to warrant the somewhat unknown risks of the vaccines or less known risks than these older vaccines? But we are using the older vaccines in diseases that are very rare. And if you think about the risk of mumps or measles or rubella or any of the other diseases (phonetic) in children where the rates are also very low and yet we continue to immunize, can you just kind of put it in the context of what the benefits would be for vaccination?

DR. HANNAH KIRKING: Yeah, it's a great question. I guess I would say that it's a good analogy, actually, one that I haven't spent a lot of time thinking about. But it's a little bit to, like, the tolerance of transmission probably and what can happen when transmission begins. And this is where I

think the risk-benefit to the individual is one way of looking at it, but the risk-benefit across the population is the other. Similar to, as you kind of allude to, a lot of the benefit of a measle vaccine in a single kid or in a cluster of children is usually to prevent outbreaks as much as it is to benefit them at the individual level. So it is a good analogy to make.

I think, again, the unknown, a little bit, is that we have some sense of transmission and what could happen with measles or mumps or rubella -- probably beyond our ability right now to predict what will happen with transmission for COVID. And so the analogy is a good one I would say.

Knowing the trajectory of what's going to happen, I think is a little bit more unknown for COVID. Similarly, though, I do think that there is -- based on what we know about children's ability to be infected and their (audio skip) as well as transmission, I do think that there is some risk for transmission in child centric populations where you congregate those who are unvaccinated, which is not totally dissimilar to things

we might consider related to measles or some of the other childhood illnesses.

So I'm not sure if I'm answering your question fully or not. It's a little hard to make a full direct comparison. But I do think, with the population versus individual considerations, it holds valid.

DR. ERIC RUBIN: No, thank you very much. I realize that it's an extremely difficult question. I appreciate your taking a shot at it.

DR. HANNAH KIRKING: No problem.

DR. ARNOLD MONTO: Dr. Wharton.

DR. MELINDA WHARTON: Thank you. I think this question is for Dr. Fink. I was glad to see the discussion of dose ranging studies in the FDA briefing document and just wanted to ask a question about that. Is it reasonable to assume that further vaccine development in younger age groups will be preceded by dose ranging studies?

DR. DORAN FINK: Yes. That's a reasonable assumption. And I believe that ongoing studies have some details published on ClinicalTrials.gov so you can

look and see what's being done with regards to dose ranging.

DR. MELINDA WHARTON: Great. Thank you.

DR. ARNOLD MONTO: And Doran, as a parallel to that question, how does that fit into the safety database?

DR. DORAN FINK: So, typically, what we would ask for is an adequately sized safety database of trial participants exposed to the dose and regimen intended for use, whether that's use under Emergency Use Authorization or use post-licensure. That number is clearly a topic for discussion today. If there are data available for higher doses -- although we would expect with dose ranging studies the numbers exposed to those higher doses would be substantially less than the numbers exposed to the dose ultimately selected for pivotal studies in specific age groups. Then we would also evaluate safety data for those vaccine recipients as well.

DR. ARNOLD MONTO: Right. I'm thinking of studies that actually lower the dose from the ones that

are typically used in adults, which create other questions. Thank you. Dr. Kurilla.

DR. MICHAEL KURILLA: Thank you, Arnold. I actually have a question related to the CDC discussion earlier today on the myocarditis. And the question is right now that adverse event seems to be largely associated with mRNA vaccines, clearly coming out of the Israeli data, which I think they mostly used just one mRNA vaccine. And we have very limited experience, at least in the younger age groups, in this country with anything other than mRNA vaccines.

What I'm wondering, though, is there any data on either the J&J or AZ vaccine in younger populations, 18 to 25, that the question is is this a class effect of the mRNA vaccines, or is this a broad adverse event related to just the COVID vaccines themselves? Do we have any clue about that?

DR. TOM SHIMABUKURO: Hi, this is Tom. Can you hear me, first of all?

DR. MICHAEL KURILLA: Yes.

DR. TOM SHIMABUKURO: Okay. I can't speak to

any AstraZeneca data. I can say there are reports of myocarditis after all of the authorized vaccines. But we're seeing this increased reporting, or unusual or unexpected reporting, is primarily after the mRNA vaccines in adolescents and young adults, mostly in their early 20s, after dose 2. And the clinical features of these are similar to what other groups have observed mainly in Israel and also in the Department of Defense data. So we think that this is something that we're observing primarily in mRNA vaccines, again, in these younger age groups.

DR. ARNOLD MONTO: And, Tom, the duration of (audio skip) -- the duration from onset -- go ahead, Mike.

DR. MICHAEL KURILLA: And I'm curious. With the preponderance in males, so when we go to a pre-pubertal group, would you assume that maybe that myocarditis would not be as prominent, or you would not want to make that estimate at this point?

DR. TOM SHIMABUKURO: Do you mean the male to female ratio?

DR. MICHAEL KURILLA: Yeah, is it associated with something that would be post-pubertal in terms of a physiologic effect?

DR. TOM SHIMABUKURO: I'm not that familiar with the specific epi of myocarditis in that group. I can say that the proportion male to female in these older adolescents and in these younger adults, it is similar to what's observed with myocarditis in general.

DR. MICHAEL KURILLA: Okay.

DR. TOM SHIMABUKURO: And I can make an assumption that might apply to younger age groups, but I don't know the answer. I don't know the specifics to that.

DR. MICHAEL KURILLA: Okay. Thank you.

DR. ARNOLD MONTO: Before you go, I just want to -- since we're going to be talking duration of follow up, this is mainly two to four days from inoculation?

DR. TOM SHIMABUKURO: So the symptom onset for most of these cases have been around four days and the overwhelming majority within a week. So there are

cases that have an onset beyond that. But in the recent cases in these adolescents and young adults, the onset has mostly been within days and most of them within a week.

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

DR. ARCHANA CHATTERJEE: Dr. Shimabukuro, actually, this is for you as well. In the dataset that you shared with us -- you shared a lot of data, so thank you for your presentation, first of all. But you went through it fairly quickly, and I want to make sure I understood this particular piece of information correctly. When you showed the cases of myocarditis, pericarditis that occurred in the Pfizer and Moderna recipients, it seemed to be more cases in the Pfizer recipients than in the Moderna group. Did I misunderstand those data, or is that a real thing?

DR. TOM SHIMABUKURO: So, for the VAERS reports, our spontaneous reporting, our passive surveillance system, there are more reports after Pfizer vaccine. In our active surveillance system, the Vaccine Safety Datalink, there are more reports after

Moderna -- or not -- more diagnoses. Those aren't reports. There are more diagnoses after Moderna. So it's a bit mixed.

DR. ARCHANA CHATTERJEE: Okay. So what piques my curiosity was if this is a class effect, as Dr. Kurilla talked about, and this has something to do with the mRNA platform, these are both mRNA-based vaccines. And so is there a difference do you think in the formulations that result in this, or are these data just too few to make those kinds of analyses at this point in time?

DR. TOM SHIMABUKURO: So there have been slightly more Pfizer doses used in the United States, and Pfizer is the only vaccine that's authorized under 18. So with respect to the spontaneous reporting, I think we need to consider that. With respect to the diagnoses in the Vaccine Safety Datalink, at this point those are still pretty small numbers. So I think we need to wait for the data to mature. In Israel, I believe these are Pfizer cases because that's the only vaccine they used. In some of the other case series,

there have been both Pfizer and Moderna related cases.

DR. ARCHANA CHATTERJEE: Thank you.

DR. ARNOLD MONTO: Thank you. Dr. Gans. You're muted.

DR. HAYLEY GANS: Thank you. I had a couple of questions also for Dr. Anderson and Dr. Shimabukuru related to the myocarditis. There was one report that I think, Dr. Anderson, you showed that talked about the myocarditis and broke it down into dose 1, dose 2. And I'm curious to know a couple of things about the dose 1 individuals. Did they go on to actually get a second dose, and how did they do with that?

And then I'm wondering if there's any data that you can share or know of about the immunogenicity if that was looked at in any of these populations after dose 1, dose 2 so we could start trying to understand if there's any predictors of who might go on and have a more robust immune response. This feels like a sort of hyperimmune response that we're seeing. And with that, the immunogenicity data, is there any data related to looking at sort of cytokine release syndrome because it

feels a little like that after COVID disease?

DR. TOM SHIMABUKURO: So with respect to dose 1 cases, who may have received dose 2, I don't have that data. That's certainly something that we can look into. Sometimes in vaccine safety we see this phenomenon where if you have a dose 1 adverse event, you don't get dose 2, or you are less likely to get dose 2. But that's certainly something we can look at. I don't have any information on immunogenicity. I'd have to defer to others on that.

DR. STEVEN ANDERSON: Yeah, and this is Steve Anderson. I would say for our data we didn't -- the rapid cycle analysis doesn't break it out by dose. It's just all doses in the rapid cycle analysis even though we have access to both doses. We could do that later, but we didn't do that in this initial run.

DR. TOM SHIMABUKURO: I'll mention in the Vaccine Safety Datalink, our surveillance is all doses as well. At least right now it is. When that separate analysis we did, which was outside of surveillance, that was an additional analysis, that broke it down by

dose.

DR. HAYLEY GANS: So is anybody looking for risk factors? I guess that's what I'm getting at. All we have is a male gender sort of preponderance. And I'm wondering. And some of this might be looked at in terms of actual dose of the vaccine, what dose was used and also the way in which we give it so the schedule if we obviously broaden that. But I'm just wondering if there's any way that we can identify risk factors, or is anyone looking at that?

DR. TOM SHIMABUKURO: So we're currently following up on the spontaneous reports, doing as rapid a follow up as we can for the reports in 30 and under. And that includes getting medical records. To review the medical records, to confirm information in the reports, sometimes we actually reach out directly to the providers to make sure we get as complete a picture as possible on these cases.

We also have a group at CDC called the Clinical Immunization Safety Assessment Project which are researchers at academic research centers and have

access to specialists. And we have pulled them in to help us review cases and also to help us assess the issue of myocarditis in general after mRNA vaccines and also look into this issue of mechanistic evidence.

So I think we will be able to get more information, at least on the individual patients, and additional information, possibly, on risk factors. But right now, we don't see any obvious risk factors other than, I would say, age, sex, and dose.

DR. STEVEN ANDERSON: And then for FDA's analysis, we haven't really begun a deep dive into the cases. We haven't identified a signal in our system yet, but the plan would be to do epidemiological analysis. And we just haven't done that yet. But your question about risk factors is a valid one. Thanks.

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

DR. PAUL OFFIT: Thank you. So this question is ultimately for Dr. Kirking, and it follows up on something that Dr. Rubin had said. So it seems to me what we're trying to do here is determine risk-benefit moving forward for children. And so, in terms of

defining the risk of vaccines, we'll discuss how many patients we're comfortable with (phonetic), how big we want those range trials to be, how long safety follow up is.

But I think the harder part of this may be the benefit part. Cody alluded to this earlier. Clearly, the numbers of hospitalizations and MIS-C cases are declining.

But my bias -- and I'm curious to hear your comment on this, Dr. Kirking -- is that it's summer. I mean, they said (phonetic) it's hard to (inaudible) winter respiratory virus. And I think come winter, we're going to see really how well we're doing in terms of population immunity.

I mean, that in concert with the fact that we have variants that are becoming more contagious, which is what bat viruses do as they try and adapt to the human population. We have first the B.1.1.7 variant, now the B.6.1.7 (phonetic) variant which are progressively more contagious which means we need a higher level of population immunity.

And the bigger thing to me is that there's 195 countries out there, many of which have never given a single dose of vaccine. We still vaccinate children in this country for polio every year even though we haven't a case of polio since the 1970s. I think we are going to have to have a highly vaccinated or highly immune population for years if not decades. And it just seems silly to think that we're not going to have to include children as part of that since they can suffer and be hospitalized and occasionally die from this virus. Three hundred children have died from this virus, at least.

Getting back to Dr. Rubin's question, there would be 500 children, roughly, that would die of measles. Far fewer die of varicella, far fewer die of flu, at least now. So I don't know. That -- my sense is (phonetic) that the notion that we are not going to have to vaccinate children going forward, I think is wrong. But I'm curious to hear Dr. Kirking's comments.

DR. HANNAH KIRKING: Yeah, thank you for the comments. And I think there is a lot of truth to it to

think about the population, what's happening around the pockets of unvaccinated kids and what that might mean -- or around pockets of children, whether they're vaccinated or unvaccinated.

I would say we can pull a little bit from some of our epi studies that we've done in the field already, where we've (inaudible) school transmission investigations. We've done some outbreak investigations in some summer camp students last summer. And the thing that overwhelmingly I think we learned from kind of investigations of what happens when COVID is introduced into a student population are two-fold.

One, in a group of children where it's introduced and there's not a whole lot of mitigation measures, it will transmit throughout. That's one thing. The second thing would be that the background community transmission definitely does affect how much introduction and transmission you will see in a child centric environment. And so just from school transmission work, we did three different locations

where we looked very closely at cases introduced and tested holistically around cases in schools. And this was before adults were as highly vaccinated as they are now.

And in general, when community background rates were higher, we found more in kids. And when they were lower, we found less in kids. And so I would say those two kind of field epi datapoints kind of go against each other. As community transmission is lower, you schools will do better even if they're unvaccinated. On the other hand, it can spread once it's introduced.

And so I think in context of your -- global aspect to your question, we do live in a fairly global society. And so having big pockets of unvaccinated, we would anticipate, potentially, some outbreaks.

I think that the other part that makes its way into this that's hard to predict is what other mitigation measures might stay or not stay. And that becomes, also, an important part of the dialog. When we did transmission investigations in schools, largely

last winter when case counts were high, the other mitigation measures work.

The other way I would say that is that last winter the rest of the respiratory viruses, with the exception of a few, were mostly quiet. So those other mitigation measures, even outside of vaccines, were effective. If we potentially are in a position where some schools or states might decide not to continue with some of those, we might see a very different pattern.

DR. PAUL OFFIT: Right. All we have to do is just mask, social distance, shut down schools, shut down business and restrict travel, and we're good. There's a price for that but (inaudible).

DR. HANNAH KIRKING: I think yours is a good point, though.

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

DR. STEVEN PERGAM: Thanks, Arnold. Thanks. Dr. Kirking, this is a question for you. I haven't seen much data in children related to the immunosuppressed population. We're looking at outcomes

of interest. It's merely focused on generalities like obesity and other demographic factors. There hasn't been as much related to the IRIS population. And in adults, that's clearly becoming a major risk factor for mortality.

I worry a little bit that as we're thinking about these data -- and I'm curious your thoughts on this -- that much of what we've come through in the initial phases, these high-risk individuals would have been not in environments like schools or in close contact and so were less likely to become potentially in contact with others that might have been infected.

But as that changes and as states become less cautious, we may be putting a number of those high-risk children at risk. And I'm curious if you guys have considered this in sort of the analysis and whether or not you have much data on hospitalizations, mortality, et cetera, in the high-risk groups that might be particularly at risk?

DR. HANNAH KIRKING: Yeah. I think in terms of your question about data on the high-risk group

specific to younger children or the pediatric population, I don't have that information right now. Definitely, we have it to some extent. And how big of data it is or how much signal we can pull out of it, I would have to talk to some colleagues that are leading analyses on that data, specifically. So my apologies for that.

I think your point is a good one, though, that there could be high-risk children out there that have been protected over the past year by other mitigation measures, whether that is distancing or school from home or tighter mask recommendations for children and/or adults. So I do think that there could be changing epidemiology coming specifically as pertains to high-risk children if that makes sense. I don't know that I can predict yet what that might look like. But definitely would expect it will change as the overall proportions of (inaudible) cases are right now is also changing.

DR. ARNOLD MONTO: Thank you. We're going to have a few more general questions before we get on to

the discussion topics. And Dr. Fuller, please.

DR. OVETA FULLER: Yes, thank you. Just a statement, and I'm not sure if this directed to Dr. Fink or Dr. Kirking. But if we think about where we've been with vaccines in this country, they could (inaudible) a lot of disease for a lot of people. We look at measles, mumps, chickenpox, HPV, rotavirus, polio, hepatitis, and we talk about COVID.

Children have been protected because they've been home as we were just talking about. And I agree with Paul. As we open up, this virus will not be in adults because adults, most of us, hopefully, will be immunized or in some way protected because of natural infection. So it's going to go to those who are not immunized. And that means the population circulation in children is going to be higher. So we already know that their staying home is not a social -- viable alternative. So I don't see that we have any option except to also protect our children in the best way we know with what we do with vaccinations in this country.

So my question is what has been -- and this

will get into the later discussion -- what has been the database size that was needed for rotavirus or Gardasil, either EUA or in those cases licensure? And what is the typical follow up? We are still, I believe, in an emergency situation.

I think that when this virus goes into our children, which is what it's going to do, that will give it an incubator to change. And so not just to protect them, which is important, but to protect ourselves as well as the global population, I agree with Paul. And I guess I'm asking what has been the precedent for looking at the number in recently licensed vaccines? And I'm not sure who is best to answer this, Dr. Fink or Dr. --

DR. ARNOLD MONTO: I'm not sure either, but this is a nice segue into the first discussion topic. Anybody, Dr. Fink or Dr. Gruber, or anybody would like to talk in response? And then we'll switch to the first discussion topic.

DR. DORAN FINK: Yeah, hi. Yeah, Dr. Monto and Dr. Fuller, I'm happy to take this question. So I

think these general considerations were touched upon in our briefing document and in my presentation and also in response to an earlier question from Dr. Meissner where I provided some examples. And he asked about some examples. But I'm happy to go over those again because I do think, in agreement, it's an important point.

So sometimes FDA approval of vaccines for use in pediatric populations has been the first approval of those vaccines. So they have not previously been studied or approved for use in adults. And in those situations, the safety database has largely been driven by considerations for adequately powered clinical endpoint efficacy trials so into the tens of thousands or multiple tens of thousands of vaccine recipients.

And so one example of that recently, was Dengvaxia, the dengue vaccine that was approved a few years ago for ages 9 through 16. There have been, on occasion, safety databases that have ranged into the tens of thousands, 60,000, under 70,000, for a rotavirus vaccine because of the desire to further

evaluate and characterize a specific safety concern and in that case, intussusception.

On the other hand, in numerous examples where vaccines were first studied and licensed for use in adults and then approved for use in pediatric populations based on an immunobridging approach, the pediatric safety database to support that licensure has been considerably less, somewhere in the range of 500 to around 3,000 or so total trial participants exposed to the dose and regimen intended for use under licensure. And that range depends on the age ranges being contemplated for approval as well as other factors.

So we talked about the example of Gardasil, the first approved HPV vaccine where we had slightly more than 3,000 vaccine recipients ages 9 to 17 in the case where that approval was concurrent with approval for use in younger adults. So really very little adult safety data other than the thousands of adults that were evaluated in the clinical trial that provided evidence of clinical endpoint efficacy. And then

several other examples, Japanese encephalitis virus, oral cholera vaccine, where we had fewer than 3,000 total pediatric recipients across age groups supplemented, of course, with data from clinical trial experience and post-licensure use in adults.

And then just to round out the answer to your question in terms of precedent for Emergency Use Authorization, we really don't have precedent. These COVID vaccines are the first ones authorized for emergency use.

DR. OVETA FULLER: But just a final comment, I think we are in an emergency situation. We haven't seen it for these children because they have been isolated or there have been other mitigations. But as we open up again, we won't have those. We don't do a very good job with those. So I think we are in an emergency situation and will be going into the winter. Thank you so much.

DR. ARNOLD MONTO: Thank you. And we are going to shift now to the answers to the questions -- or the discussion of the specific questions. So the

first one up on your screen, "Provided there is sufficient evidence of effectiveness," we are going to be talking about two age groups, 6- to 12-year-olds and 2 to less than 6 months of age -- and three groups, 6 to 12 years, 2 to less than 6 years, and 6 months to 2 years. We're talking both about safety data in terms of sample size and duration of follow up. And we're talking about Emergency Use Authorization and licensure.

We also heard in Dr. Fink's introduction that it is possible that we may say that we only want to work towards licensure, that Emergency Use Authorization is not necessary in a particular age group. So I'm opening up the floor to discussion. Dr. Meissner, you're first.

DR. CODY MEISSNER: Thank you, Arnold. It's a very interesting conversation, but I have a couple of comments. And first, I want to start off by thanking Dr. Fink and Dr. Gruber and others at CBER for their extraordinary leadership during these very, very complicated discussions. And I can't think of anyone

who has more integrity and is more thoughtful than you folks are. So thank you for everything that you've done.

I agree with Paul Offit. I think we certainly need a pediatric vaccine. That's not the question that we're discussing today. The question, in my mind at least, is at what point will we have sufficient data to justify a pediatric vaccine? Because, after all, children grow up to be adults and we want them to be immunized and immune.

But remember, people keep citing high rates of disease in children. The rates in children are four -- the hospitalization is four hospitalizations per million children under 18 years of age. That's on the CDC website. That is not an emergency. It is a very low hospitalization rate. And the rates may change as the season changes, but we're starting from a tiny, tiny rate. And I would -- the rates are also falling pretty dramatically among adults and children. So as more people are immunized and become immune from infection, I think it's very likely that we're going to

get this pandemic under pretty good control.

Now the issue -- so the issue to me is safety. And I don't -- we can look at the 2,000 or 2,200 adolescents who are enrolled in the Pfizer vaccine between 12 through 15 years of age -- 2,200, so half got the vaccine, half got placebo. Nobody was hospitalized. Nobody died. And there were some who got URIs (inaudible). So 2,200 is not going to address the issue of safety.

I'm worried about myocarditis. And let me just make a comment because I've spoken to a number of cardiologists about this. The way we evaluate myocarditis today is based on gadolinium enhancement of an MRI in a person who has chest pain, elevated troponin levels, tachypnea perhaps. And this method of diagnosing myocarditis is very, very sensitive. It doesn't take much of an insult to the myocardium to get a positive gadolinium scan.

But we don't know what that means on a long-term basis. Will there be scarring of the myocardium? Will there be a predisposition to arrythmias later on?

Will there be an early onset of heart failure? I think that's unlikely, but we don't know that. And so before we start vaccinating millions of adolescents and children, it is so important to find out what the consequences are because COVID-19 disease is disappearing in adolescents and children. And I think we have to be so clear about what we're dealing with.

Let me make one more point. In 2003, there was a publication in *JAMA* regarding myocarditis following the Dryvax vaccine, the smallpox vaccine which is, of course, a live vaccine. But in that situation, the military -- it was given to young recruits. The rates of myocarditis in the military young men -- because it was mostly men in those days -- was 2 per 100,000. And after the Dryvax vaccine the rates were 7.8 cases of myocarditis in the 30 days afterwards. So there was a three-fold increase. And in fact, Dr. Tony Fauci wrote an editorial in that same issue of *JAMA* discussing these rates of myocarditis.

So I am really concerned that the FDA may by not insisting on a full BLA, which to me means at least

12 months, maybe even 18 or 24 months of follow up in children and adolescents, before they are recommended to receive this vaccine. I do not feel we can justify a EUA including children under an Emergency Use Authorization. The burden of disease is so small, and the risks are just not clear. We don't know. Once we've clarified it, then we definitely want to go ahead with this immunization program.

There are other problems as we've mentioned. We don't know what the risk is with co-administration. What happens if it interferes with other vaccines? I don't think it will. It's hard, as has been said, it's hard to imagine a biological explanation, but it has happened with other vaccines. So I think caution should rule the day here. Thank you, over.

DR. ARNOLD MONTO: Dr. Meissner, before you leave, are your comments up to 18 years of age?

DR. CODY MEISSNER: Yes, sir, they are. I'm uncomfortable about administering because so few children up to 18 have been enrolled. And we admitted a 12-year-old boy over the past weekend, two days after

his second mRNA vaccine, with a troponin level greater than nine, very high level, and evidence of myocarditis. This is not -- I cannot believe this is a random occurrence. There is an occurrence. It has to be included in an informed consent if we're going to move ahead. I think it needs a very careful safety evaluation before we recommend it because the risk of disease is so low in this group. Over.

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

DR. OFER LEVY: Hello, and -- yeah, thank you for the opportunity to make some comments. I wanted to make some comments about the big picture, pick up on some of the themes that Paul Offit brought up. I think it is a very complicated series of considerations in the big picture. And we've heard a lot both in the public commentary and now from Dr. Meissner about the very cogent arguments to go slow, be careful, and keep in mind the relatively low burden of disease.

On the other hand, as Paul pointed out, we're reaching summertime here, which is the nadir for most respiratory viruses. I think the truer test will be

how do the fall and winter look? We've got to keep that in mind.

I know we're not focusing on variants here, but they're out there, and some of them do spread easier. And so we have to keep that mind. And finally, from an ethical perspective, while it's true that we have to focus on the benefits to the population that we're thinking of providing a vaccine for, in the case of children, reaching herd immunity as a nation across all age groups also directly benefits children because the economy opens up, schools open up better. And so I think it's a very complicated topic. The themes have been touched on, but I wanted to put that out there on the big picture.

More specifically, in terms of the clinical trials -- and I know there's been some of this -- the dose ranging and the granularity of the doses may be very important with the mRNA vaccines. And I hope FDA continues to work with the sponsors to encourage granularity in dosing and follow up to see if they can hit sweet spots where one benefits from the

immunogenicity and perhaps less of the potentially associated myocarditis or other adverse events of special interest.

And then from a research perspective and a very important translational perspective, let's try to better understand what this potential association with myocarditis is. Our research group, at the Precision Vaccines Program and others, Mihai Netea in Europe and others, have opened up a field of innate memory. It's logical we measure the antibody response to the mRNA vaccines to the spike. We believe that protects us.

But these vaccines also alter the innate immune system. And Mihai Netea just posted a study from immunized adults that shows that if you take their blood after mRNA immunization, mRNA vaccine -- this was the Pfizer product -- there is altered innate response in the blood to stimulation with pattern recognition receptor agonists like TLR agonists. So these vaccines may have innate immune altering effects, and that could conceivably relate to myocarditis. That's just theoretical, but we know, for example, with viral

myocarditis that these same innate pathways are triggered. So that's a possible connection.

But my question to FDA is what is the possibility of encouraging the sponsors to gather more information about the innate immune activating effects of these vaccines because more needs to be learned about that. So those were several opinions, but they ended up with a question to FDA in terms of what are their interactions with the sponsors around understanding innate immune effects of the vaccine?

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

DR. DAVID KIM: Well, I certainly appreciate the perspectives that Dr. Offit, Dr. Meissner, and Dr. Levy just presented. And I'd like to add a comment, just a very simple -- actually a rhetorical question.

There is a cost. And we've seen that -- with myocarditis and other rare side effects -- that there is a cost to vaccinating the population. And I think we should also consider -- and I'm sure that's what all the members as well as the watching public are thinking as well -- what is the cost of not vaccinating? What

is the cost to our children if we do not proceed with a vaccination program, not only in terms of protecting their health, but for the larger public health? So I throw that out there for consideration.

And I have a question for Dr. Fink, and perhaps Dr. Anderson can also comment. In the adverse event evaluation -- the, perhaps, post-marketing evaluation -- that there's a comparison group. And Dr. Fink mentioned that the comparison group will be followed as long as feasible and also, that numbers like that that Dr. Fink presented that identified median of six months, or what have you, as a follow up.

To contextualize these issues, vaccine confidence, vaccine acceptability and vaccine uptake, they're all closely related and they move in the same direction. And the more we can do to promote acceptability, confidence, and promoting the use of the COVID vaccine, the better off we're going to be in the long run, obviously.

And towards that, vaccine safety has been identified as one of the primary, if not the primary

reason, why there is a lag, perhaps, a lag in the use of vaccine and in gaining vaccine confidence and vaccine acceptability. So the more we can do to promote confidence in addressing the risk of COVID-19 vaccine, the better off we're going to be.

So what I'd like to ask Dr. Fink and Dr. Anderson -- that I realize that there's precedence, there are set languages that we use. But COVID-19 is obviously not -- does not allow us to get fixated on what was done in the past, necessarily. So moving forward, I wonder if you would consider using perhaps a different frame of reference for discussion question one?

It also applies to the second and the third questions regarding the duration of follow up. And that is rather than using follow as long as feasible, what if FDA were to be more prescriptive in saying that the adverse event evaluation in the comparison group should be followed for at least a year, at least two years -- something akin to what Dr. Meissner was saying earlier, perhaps as long as three, four, five years to

allay the public about the fears of not knowing or not addressing the long-term effects, long-term adverse effects of COVID-19 vaccination program?

And by the same token, rather than -- there were several slides that Dr. Fink presented. I think the first one was slide number 10, 11, 12, somewhere around there, where median was used, median of -- and what if we replaced the word "median" follow up with minimum of six months so a median of six months versus a minimum of six months to again -- of course, this would delay the outcome analysis by several weeks. But, again, this would help reassure the group -- the providers, and the public that a more definitive set of guidelines or set of rules are being used to ensure vaccine safety and promoting the use of vaccines for the public.

DR. ARNOLD MONTO: Before you answer, Dr. Fink, may I just add an additional point? And that is without either Emergency Use Authorization or a licensure with the event frequency that we have, how many cases will we have to evaluate over these time

periods? Because I think that becomes an issue as well if we have the kinds of numbers that are going to be in (phonetic) these evaluations before either Emergency Use Authorization or licensure. And is the solution some better kind of post-marketing surveillance to answer some of these questions simply because of the low frequency of these events? Please.

DR. DORAN FINK: Thanks, Dr. Kim. So let me try to answer your two questions in order, first, the language of "as long as feasible" for evaluation of the control group. So this is a theme that is repeated from our October VRBPAC meeting and our product specific VRBPAC meetings for authorization for use in adults and, in the case of the Pfizer vaccine, going down to age 16.

The reason we say "for as long as feasible" is because once a vaccine has been authorized for emergency use by FDA and recommended for use by CIC (phonetic), if one were to then insist that all trial participants who were originally randomized to placebo remain in follow up without access to the vaccine, then

you run into serious ethical issues. And we've heard a number of very strong viewpoints expressing the reasons why that's problematic.

So when we say "as long as feasible," that's not to suggest that those control recipients would cease to be followed at all in the trial. It means that at some point when the vaccine is made available and recommended for use, it becomes very difficult to argue against providing access to that vaccine to the placebo recipient. And so, ideally, that access would be given under the conditions of participation in the clinical trial, and they would continue to be followed in the context of the clinical trial.

DR. DAVID KIM: If I may, but in the context of what we were discussing in earlier VRBPAC meetings as far as the unmasking of the control group, I think they were to be offered the vaccine for crossover monitoring. And along those lines there would be those who have not received the vaccine.

And so I'm talking about an opportunity where there's a reasonable chance that we may be able to

study -- a long study -- adverse events occurring over a longer period of time. That rather than self-limiting the duration of follow up with as long as feasible, to be more prescriptive in identifying a period of time that would suit, that would allow us to gain more information for long-term adverse events.

DR. DORAN FINK: And I do think that we're on the same page, that we do want all trial participants to be followed for a long as possible, whether they are initially randomized to vaccine or randomized to placebo and then at some point choose to be unblinded and crossed over if the vaccine could be made available and recommended. So I couldn't agree with you more that having as robust a duration of follow up as possible is important.

Having said that, there is cost to waiting for very long follow up before taking any kind of a regulatory action to make a vaccine available. And so we do have to be realistic about the duration of follow up that we would expect prior to (audio skip) warranted considering that. And remaining follow up would need

to be done after authorization or licensure as well as in the context of post-authorization or post-licensure use.

The other question that you asked was about this notion of a median of six months of follow up. Here, the intent was to really be parallel with the framework that we established and that the VRBPAC endorsed back in October for clinical trials in adults. Clearly, those adult efficacy trials have many more trial participants than an immunobridging trial in a specific pediatric age group would have.

But in presenting the numbers that we've discussed with vaccine manufacturers in terms of overall safety database and numbers for specific age groups, those numbers actually do reflect what would be potentially an acceptable number of vaccine recipients with at least six months of follow up. So if you take 1,000 vaccine recipients with a median of at least 6 months, that means at least 500 (audio skip) vaccine recipients (audio skip) for a specific age group.

If your concern or your interest is detecting

very rare adverse events, then increasing from 500 subjects with at least 6 months to 1,000 subjects with at least 6 months really isn't going to accomplish anything. Increasing to even 10,000 would likely not accomplish anything either and thus the need to consider what additional safety evaluation could be accomplished in the post-authorization or post-licensure period.

Additionally, when thinking about prolonged duration of follow up prior to making a vaccine available, again, the question is are there specific events that would not become apparent or would be difficult to characterize in a reasonable number of subjects that could be evaluated in the pre-licensure period with a much longer duration of follow up? The concerns that we're talking about now largely manifest in the fairly short-term after vaccination.

And so I think we're right to focus on those concerns. But I think we need to be realistic and really question what additional information would a much longer duration follow up prior to making the

vaccine available, what information would that provide in terms of the benefit and risk? Thank you.

DR. ARNOLD MONTO: Thank you. And then I'm getting alerts that we have 15 hands raised, and the clock is moving on. So I'm going to move on. I think the critical thing we heard was with an infrequent outcome -- and we'll use myocarditis as an example -- long-term follow up of the small number of events isn't going to give us a whole lot. And that is our dilemma. In terms of not having approval or licensure, then if you don't have use, then you're not going to have events to follow. And I recognize the problems that that creates.

Dr. Rubin, please. And I hope you're -- from now on, since so many people have their hands raised, please try to keep your questions focused -- or comments. They don't have to be questions.

DR. ERIC RUBIN: Thanks, Dr. Monto. I've heard what people said, and I listened carefully to what Dr. Meissner said. And I agree with all of his suppositions and come to completely the opposite

conclusion. Remember here that we are deciding whether or not this vaccines becomes available. We're not deciding how it's used.

And as we've heard from a number of people, there's not much disease right now. It's not clear in the fall whether or not this will be a useful vaccine. But I will point out that we use a lot of vaccines for which there's very little disease, as Dr. Kirking mentioned, for public health reasons. We don't think that that's a -- we are willing to make that trade off with an individual benefit versus a community benefit. But, sure, we don't know what's going to happen. I think that's precisely the reason why we want to have these in our arsenal.

Because we give an EUA to the vaccine, doesn't mean we have to use it. And I think we would have to think hard about how to use it given all of the concerns that have been raised. But just to follow up with on what you just said, we're never going to know. Remember that the data that Dr. Shimabukuro presented shows that these huge confidence intervals are not even

-- we're all worried about myocarditis. We're not even sure that it's an association right now. It's very hard to tell. And that's over hundreds of millions of doses given in the U.S. alone.

The last thing I'd say about safety is this isn't a blank slate. We're not going in with a new vaccine to kids. We're going in with a gigantic base of experience now in adults. And that experience has suggested that there may be rare side effects. But there aren't common side effects, at least for the mRNA vaccines or actually for any of the vaccines at this point. So our prior probability going into this of having side effects that we're really going to miss, even in the smaller studies that we're talking about, is low.

I hate to not have the tool because, as people have said, when we get back in September and kids are back in school and people are back indoors and in certain parts of the country vaccine rates are very low, who knows what things are going to look like? And I would just like to have the ability to use this

vaccine if we need it. If now we set preconditions that are not achievable over a reasonable amount of time, we won't have it.

DR. ARNOLD MONTO: Thank you, Dr. Rubin. Given the number of people who want to express their opinions and the complexity of the questions we have and their multiple parts, I think it might be useful first to look at the three different age groups that are involved in this question and try to comment on whether there would be different answers to each of the three different age groups, let's say starting from the bottom, the under six months to two-year-olds and working our way up to try to come to some degree of consensus of importance to have the vaccines, as Dr. Rubin just said, available for use.

So I'm going to ask everybody to lower their hands and try to focus on that question so that we can try to move forward and come to some kind of, if not consensus, then a variety of different opinions so that the Agency can be informed by our opinions. So now anybody who wants to comment, Dr. Cohn, you got there

first.

MR. MICHAEL KAWCZYNSKI: And then, Arnold, just a reminder every once in a while, if you don't mind turning your camera on?

DR. ARNOLD MONTO: Okay. Yeah, I'm hiding.

DR. AMANDA COHN: Thanks. To echo Dr. Rubin's comments, I also agree that continued duration of follow up does not help us in this situation in terms of having confidence, in terms of the safety for these age groups. So I also came to an opposite conclusion as Dr. Meissner, and that it's not duration of follow up that I'm concerned about, it's the size of the cohort that's studied.

And I think when you break it down into age groups, you could potentially consider, as you get younger, asking for an increasing size of a cohort to study. So 1,000 may be sufficient for 6- to 12-year-olds who are more like adolescents. But we may want to expand the cohort size as we get into that younger group where there are such -- can be differences even by year of life.

DR. ARNOLD MONTO: And as we go through this, we have question number three -- or topic number three, which is a follow up after approval or licensure. Keep that in mind as something that's going to be there after we either recommend approval or licensure. Dr. Offit.

DR. PAUL OFFIT: Right. I agree with Drs. Cohn and Fink and others regarding that the issue is not one of how long we follow up but how many people we want to follow. And with that, it comes to what level of risk are we willing to accept? At some level, having lived through the rotavirus experience, I think it is instructive. The RotaShield was introduced in the United States in 1998 and was found to be a rare cause of intussusception, roughly 1 per 10,000, 1 per 30,000 infants -- this was given at 2.6 months of age -- developed intussusception.

For a disease that killed between 20 and 60 children a year in the United States -- babies a year in the United States, that was considered unacceptable. That risk was considered unacceptable even though you

probably had a 5 to 10-fold greater risk of dying from rotavirus in the U.S. than dying from intussusception, that risk was considered unacceptable.

And so two more trials were done seven to nine years later. The first with RotaTeq was 70,000, the second with Rotarix was 60,000, which then ruled out a risk that that -- ACIP was comfortable with saying, okay, we don't have this level of risk. But then when those two vaccines, both RotaTeq and Rotarix, got into the real world and were given to hundreds of millions of people, we found that those two vaccines also caused intussusception but at a much, much lower rate than was seen with RotaShield.

So it's not an issue of avoiding all risk. It's an issue of what level of risk are we willing to accept, which is going to dictate how big we want those trials to be. And I agree it is not amount of length of follow up, it's a matter of what the size is. And those size are going to be determined (phonetic) to some extent by the different age groups which then have different risks regarding just COVID itself (phonetic).

DR. ARNOLD MONTO: And would you suggest some numbers? I put you on the spot.

DR. PAUL OFFIT: I'll pick a number.

DR. ARNOLD MONTO: Yeah, okay, you pick a number anyway.

DR. PAUL OFFIT: Younger children, I would think -- I will say 10,000. As you get to older children, I would be between 5- and 10,000. But I'm making that up and didn't have much time to think about. I would love to hear what other people think, especially Dr. Fink, about what numbers they would be comfortable with.

DR. ARNOLD MONTO: Dr. Chatterjee or Dr. Fink, do you want to jump in?

DR. DORAN FINK: I think we're interested in hearing the discussions of safety database size and input from other members of the VRBPAC to help inform our perspective in our decision making. I think we've laid out what we have accepted in the past for other preventive vaccines authorized for use in these age groups. And if there are compelling reasons to take a

different approach for these vaccines, then we would like to hear those.

DR. ARNOLD MONTO: And in some ways, given that this is age de-escalation, these are not going to be parallel in terms of age groups necessarily because that's another consideration. We will have information from the previous one, correct?

DR. DORAN FINK: Correct.

DR. ARNOLD MONTO: Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Thank you, Dr. Monto. I have a couple of quick comments to make and actually a couple of questions. It's interesting that I was going to bring up the rotavirus experience, Paul. So I'm glad you went through that because that is informative, I think, in terms of us understanding the numbers you need in a database versus how much risk we can tolerate?

When I saw this issue come up -- and it's still up there on my screen -- I looked at the database size and I thought to myself, more and for the duration, longer. And those were originally (phonetic)

the only two things that came to my mind. Jokes apart, I think that this requires probably some sort of statistical modeling to help us understand better what the database size actually needs to be.

I agree with both Dr. Cohn and Dr. Offit that as you get to the younger age groups, you probably need more to be able to pick up at least on some of those less frequent adverse events.

I also think it's important for us, especially in that six months to two year cohort, Dr. Monto, that we do consider concomitant use of other vaccines. Because the vast majority of pediatric vaccines are actually administered in that age group.

And while there may or may not be interference, there may be increase -- from a safety standpoint, there may be increased adverse reactions that occur. I think that in order to have some confidence in saying that those things are not likely to increase the adverse events that occur in that age group, I think it would be important to have a bigger cohort in the younger age group.

DR. ARNOLD MONTO: Thank you. Dr. Sawyer. I think you're muted --

DR. ARCHANA CHATTERJEE: We can't hear you, Dr. Sawyer.

DR. MARK SAWYER: All right, thank you letting me make a few quick comments. I do agree with those in general who think we need these vaccines sooner rather than later in children. I think that it's really challenging to predict what's going to happen with this infection. And I'm pretty sure we're going to need the pediatric component of immunity to create the herd immunity we need given the number of unimmunized adults that are still going to be around given what we've seen so far.

Obviously, we need to follow the myocarditis story very carefully, and that might change the equation. I'm going to put out a lower number than Dr. Offit did. I don't think we're going to find rare side effects in the clinical trial easily and especially the really rare side effects as has already been stated. And so I'm thinking something in the 3- to 5,000 range

would tentatively make me comfortable. We have very robust safety systems for evaluating vaccine post-use, post-release, licensure or EUA. And those will capture unusual, middle to very rare side effects.

And the last thing I'll say is that on a relatively minor point for the very youngest cohort six months to two years, we need to have a big enough database to have a very good sense of fever after vaccine because that's an age group where febrile seizures are common. And when we get to coadministration with other vaccines, we're going to aggravate that. And that is a public perception issue that is going to undermine confidence. So I really want to be comfortable in knowing what the rate of fever is after vaccine in the youngest cohort. Thank you.

DR. ARNOLD MONTO: And, Dr. Sawyer, just to clarify, you're talking about vaccinated individuals and not vaccinated plus placebo?

DR. MARK SAWYER: Yes, I'm interested in -- well, I'm interested. We need a comparison of fever in

vaccinated persons in order to really (inaudible) --

DR. ARNOLD MONTO: Right. But when you come up with the numbers of 3,000 to 5,000 or something like that, that's vaccine recipients?

DR. MARK SAWYER: Yes, but as Dr. Offit did, I also just made up this number, obviously.

DR. ARNOLD MONTO: Well, obviously. That's the problem. Dr. Fink, yes.

DR. DORAN FINK: And can I also ask for clarification? Are you talking about 3- to 5,000 per age group, or are you talking about 3- to 5,000 overall appropriately represented by various age groups?

DR. MARK SAWYER: I was thinking overall. But in terms of the last part of your question about appropriately represented, I'm certainly interested in the notion that others have already stated, that the younger group may need a slightly larger representation to find things. And so it may not be evenly balanced across the age spectrum.

DR. ARNOLD MONTO: Thank you, Dr. Sawyer, that's very helpful. Dr. Wharton.

DR. MELINDA WHARTON: Thank you. I share others concerns about the unpredictability of the current situation. I think we can't assume that disease will stay low. And I'm very concerned that as children return to school, as things continue to open up, and as we go into fall and winter that we could have a very different epidemiological situation and really need the tool of a vaccine for children. So I do think there's urgency for the pediatric vaccine development to proceed in a stage-wise manner from the older age groups to the younger age groups.

I think one extraordinary difference in this program is the very robust data we have on use of the current vaccines with hundreds of millions of doses given. And so we're adding incremental knowledge to already a very large and robust database on safety and efficacy. So I actually am quite comfortable with the approach outlined in the FDA's briefing document with safety databases of 1,000 in each of the three proposed age strata and the proposed follow up of a median of two months for the EUA and six months for licensure.

I think that's thoughtful. And it seems like the challenges of doing larger clinical trials could result in a process that was so much slower that there would be risks that we would not have these tools available when we need them.

DR. ARNOLD MONTO: Thank you. Dr. Gruber, you have your hand raised, I notice.

DR. MARION GRUBER: Yes, I just wanted to make a comment that, however, was just made by Dr. Wharton. And because I'm very appreciative that the Committee really takes courage to throw out numbers here, and we have asked (phonetic) to do so. At the same time, of course, we're hearing we need the vaccines. We need them soon in children because we do not know what the virus will be doing in fall and kids are back in school and people are indoors.

And we are in a very difficult position at FDA to really weigh that, the availability with the desire to do clinical trials in thousands of pediatric subjects. So I wanted to actually now echo what Dr. Wharton just said, there is going to be the very

difficult balance to strike. If we wait too long and do these large clinical trials with large numbers of pediatric subjects, we may not be ready to have these tools available when we need them.

And I had one more question. And that is when people say we need these vaccines available because we cannot predict this virus and what will happen in fall, is the thinking that we would need them available for all these pediatric age groups that we're discussing here, i.e., 6 months to 18 years of age? Or can we say let's have the data, let's accumulate the data for -- and I'm now making this up -- 5- to 12-year-olds and perhaps in 2- to 5-year-olds but leave the very young, the infants and toddlers out of this equation for now? So I would like for the Committee to comment on that and clarify that. Thank you.

DR. ARNOLD MONTO: Thank you, Dr. Gruber. Could I get some help, Mike? I lost my connection. Could you call on the next speaker, please?

MR. MICHAEL KAWCZYNSKI: Sure. Looks like Pamela McInnes.

DR. PAMELA McINNES: Yes, thank you. I agree with a lot of what Melinda had to say, and several other people. I want to view this as a really phenomenal opportunity right now, while some of the disease pressure is off, to actually gather the data. Let's get them. At least let us have very well characterized safety profiles in these different populations.

If I understand the May 10, 2021 extension to 12-year-olds -- and maybe Dr. Fink can clarify this for me -- but I thought there was something like 2,250 participants split between vaccine and placebo in a randomized control trial 12-to-15 years of age. And you had safety follow up for a median of two months following second dose. And then you had your immunogenicity was non-inferior to the older age group, and you had the number of cases. So those parameters came together. So if, I think, they were split 50-50, something like 1,150 people received vaccines?

If that's true, I don't think that number can be smaller for any of the individual groups. And,

hopefully, it would be a little bit bigger. I don't think it needs to be unreasonably bigger, but I don't think it can be less than what you did for extension to 12-year-olds. And this was done and so this set a precedent. And I think we have more comfort in 12-year-olds being physiologically closer to the (inaudible) database we have now in adults than we do for younger children. So I really think it's got to be bigger.

Do I think it needs to be 5,000? No. So I think you might be looking around at a minimum of 1,500 vaccine recipients in the next group down.

In answer to Marion's question, I'm very uncomfortable with having a priority focus on Emergency Use Authorization for this vaccine type in the current situation and in pediatrics. And if we took the time to say this is not going to be the priority under EUA but rather to focus on the quality of data and the amount of data that would hopefully support actual licensure, I think takes a little pressure off, assures quality of the study, and paces things.

Not everything can be the priority. So I would focus on the next step down in children, and I would like to gather the data, with time, in younger children and in toddlers, but it would not be my highest priority right now.

DR. ARNOLD MONTO: Before you go, Dr. McInnes, could you say whether your preference of not using Emergency Use Authorization go (phonetic) is in all three age groups?

DR. PAMELA McINNES: It is.

DR. ARNOLD MONTO: Okay. Dr. Nelson.

DR. MICHAEL NELSON: Thank you. This is a tremendous conversation, extremely important. Let me first state -- by stating that waiting for a crisis to pursue EUA might be dangerous for us. So I agree that we don't need to make it the focus of the conversation. But I do think we at least need to lay the groundwork and pathways so that an EUA could be enabled should the need arise in the future.

Dr. Gruber, I'm laughing because I had the exact same age group distinctions set down for me as

well. Taking into social considerations of the highest risk category as we enter into the fall season, I do believe that 5- to 12-year age group is probably the one that we should focus on. And the discrimination between ages five and six is probably going to be fairly minimal. I would not lump the six-month to age five group together. I would certainly keep them distinct in the current ones of the two -- two years of age and keep two to five years as a separate group.

Those lower two groups, I think do need larger numbers given four criteria or four emergences over the last several months with a decreased tolerance, from compassionate testimony from the public and what we've heard, increased appreciation of rare adverse events, as we've heard during the discussion today. And certainly, the increased complexity of coadministration and the ability to actually discern safety data in the midst of coadministration is going complicate matters significantly. And I think we're going to need larger numbers for that.

And the other factor that may not have been

the case in previous vaccine approval is the reliance on immunobridging. So I think, combined with those four factors, we are going to need larger numbers particularly for the two lower age groups, maybe not as necessarily for the age 5 to 12 group, or maybe we can get away with 1,500 or so. But I think you're looking closer to 3,000 for those two younger age groups in my estimation.

And I do want to give a word of thanks to --

DR. ARNOLD MONTO: Total or age group?

DR. MICHAEL NELSON: Say again?

DR. ARNOLD MONTO: Total or group?

DR. MICHAEL NELSON: So the --

DR. ARNOLD MONTO: The two younger ones.

DR. MICHAEL NELSON: The two younger ones. I think it's 1,500 each just to be perfectly honest --

DR. ARNOLD MONTO: Okay. Thank you.

DR. MICHAEL NELSON: -- is my recommendation. I do want to state and congratulate the FDA for paying such close attention to rare adverse events to vaccine and the transparency with which they're approaching

this issue. Fully appreciate you're not going to power study to identify them a priori, but laying the groundwork to be able to follow them over time is important.

Having been engaged in the rollout of the smallpox and anthrax vaccinations and seeing the similarities emerge that have, once unpredicted and probably low risk, a side effect actually turned into something that really informed how the vaccine was used programmatically is the direction we need to go. And I wouldn't jump to conclusions with regards to mechanistic studies but enable them by having high quality studies that actively assess for the symptoms of myopericarditis and actually also stratify those case definitions.

Our experience with adjudicating cases of suspected myopericarditis was very difficult, and it remains very difficult. And it can be very gray in the way of distinguishing (inaudible). So I would encourage not dismissing the prehospitalization group that actually develops myopericarditis because we don't

know what those outcomes are. And putting active surveillance in that looks for that prehospitalization (inaudible) group is going to be important for our understanding of risk.

DR. ARNOLD MONTO: Dr. Dodd.

DR. LORI DODD: Okay, can you -- I don't know if you can -- okay, thank you.

DR. ARNOLD MONTO: We got you.

DR. LORI DODD: All right, great. So I just want to say a few things. First, I agree the assessment of risk is clearly a moving target, and we do need to be ready to quickly make decisions should the risk-benefit pivot. But when I hear numbers thrown around like 1,000 to 1,500, as a statistician, I'm sort of scratching my head asking what are we going to learn with that additional 500? And if we're talking about (audio skip) really not going to learn much of anything.

And so one question back to the Committee is what are you expecting to learn with the additional 500? Even if you go up to 5,000, I would argue there

is something additional gained, but I think we would need to understand from you all what it is we're trying to gain. And then we can come up with an appropriate sample size. So from where I sit, I don't see a big difference from 1,000 to 1,500 in terms of what we would gain.

And I guess I would like to ask Dr. Anderson from his perspective as somebody who's been doing a lot of thinking about the monitoring post-marketing, if we do have these rare events, then what we need to do is really just make sure we're monitoring these things very, very closely, where we'll get lots of vaccinations. And then we're going to monitor for these rare events. So that was one question for Dr. Anderson in terms of the tradeoffs between adding more to a randomized control study that in my assessment probably doesn't add much to our risk assessment, at least for the rare events that we're talking about.

And then the other question is we're going to learn a lot from the recent rollout of vaccinations to the 12+ age group and surely that's going to tell us

something from the post-marketing surveillance of those. And so I think as that rolls out, we're going to learn something, and we're going to have to adapt our thinking. So I don't know, Dr. Anderson, if you wanted to comment on the post-marketing surveillance and if there needs to be any enhancement of that monitoring or how you make the assessment of that relative to adding additional participants to a randomized controlled study. Thank you.

DR. ARNOLD MONTO: Yes, and Dr. Anderson, we do have a third discussion topic on enhancing surveillance post-marketing, and that really does become an issue here.

DR. STEVEN ANDERSON: Yeah, so I agree. So I think your point is well taken, Dr. Dodd, about the difference between 1,000 and 1,500. And so I think, as we mentioned in my session, I think we have coverage of about 10 million children in our databases. And then if you probably stratified by sort of those three age groups, in the question, then, you're getting down to a couple million for each of these groups.

So febrile seizures, for instance, we did studies in the Sentinel System, and I think there were 2 million children involved in each of those studies. We did two of those studies, and so that's generally the power we have for these age groups. And so I think for the rare types of events, we would have coverage in the post-market systems. But, again, it's post-market versus pre-market or pre-licensure or pre-authorization is what we're talking about. That, hopefully, gives you an idea about numbers for post-market surveillance.

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

DR. MARK SAWYER: Well, to add to the discussion about staging the age groups, I agree with others that the 6- to 12-year-old is the most important. The social, educational, and mental health impacts have been dramatic in that age group. And we haven't talked much about that, but I think the long-term implications of that are likely to be profound. It's another reason I think we need the vaccine sooner rather than later.

But I do want to also emphasize the two- to

six-year-old group as important. This is a key age for social development in children. And if they need to be socially distanced or kept at home because they can't yet be vaccinated, I think we're contributing to that problem. I have a two and a half-year-old grandson, and when I take him to the park, he looks at the socially distanced and masked other children like they're from outer space. And he doesn't play on the play equipment. He's too busy trying to figure out what those other beings are in the park. So I think that age group needs to be prioritized as well.

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

DR. STANLEY PERLMAN: Yes, so I just want to add that I agree with the last statements that have been made. I think that we need to be prepared to have EUAs ready to go if we start seeing a big upsurge in number of cases in the fall.

With the number of variants that we're seeing -- I know we're not supposed to discuss this -- but the number of variants we're seeing, the kind of immune responses we measure in people who are older and also

in people immunocompromised, I think we just have to be in a good position to protect the general population in addition to children.

I know one of the comments that I was going ask earlier was in the EUA one of the public speakers mentioned that we only could consider effects on the individuals themselves and not on society. Is that correct? Because it seems to me that this is -- for children this is such a broader issue, and it's so much more important than just on the individual.

DR. ARNOLD MONTO: Dr. Meissner, your hand is raised.

DR. CODY MEISSNER: Thank you, Arnold. And I'd like to make a few comments in response to what we've been discussing, and it's fascinating. First of all, I don't think anyone disputes, again, that we need a vaccine for children. That's really not the issue we're discussing. The issue it seems to me is at what stage are we going to say we know enough to justify widespread use of a vaccine in adolescents and children?

Now, the fact that the rates of disease are falling are almost very likely related to a combination of the vaccine and natural immunity. As has been stated, about 55 percent of the population has been fully vaccinated. And there's another 20 percent or maybe more who have been infected. So we're getting up around 70 or 75 percent immunity.

So this fall, could it come back? Sure, it could come back. But the likelihood, I think, is pretty low. And there certainly are studies that say children were safer in school this year rather than the children who were kept out of school, kept at home. And a lot of that experience came from private schools, resulting in inequity among the opportunities for our children.

So I think we want to be very careful about the argument that we want to vaccinate children, again, to protect adults. Yes, we need herd immunity, but we're probably going to get there. That's what the experience was, I believe, in Israel that as more and more adults were immunized, there was less and less

disease in children. So the first mandate is to do no harm. And we don't know if we're doing no harm.

Now, in terms of the number of subjects to be enrolled, that's a very difficult question because 10,000, sure, it's better than 5,000 which is better than 3,000. But we're probably talking about adverse events that are very infrequent. And in Israel, I think myocarditis was suggested at 1 per 6,000. Well, we're not going to pick that up even with 10,000 subjects enrolled. I think this becomes a very, very complicated question.

But I think -- and hopefully we'll get more information, as was suggested, from our experience with the 12- to 15-year-old age group. Because if -- we'll see what happens with myocarditis there. And we can then make maybe a better recommendation about looking at younger children. But, again, I think even though it's not a statistical signal about myocarditis, the fact that it's so specific a few days after the second vaccine and it's in certain age group and gender, it's hard to say that that's (audio skip) over (audio skip).

DR. ARNOLD MONTO: Dr. Gruber. Dr. Gruber. I'm having some difficulties here.

DR. MARION GRUBER: I didn't mean to say anything.

DR. ARNOLD MONTO: Oh, okay. Your hand was raised in my -- okay, Dr. Gans.

DR. HAYLEY GANS: Thank you, for calling on me. I really appreciate it. I wanted to add a few points. I wanted to add in on the side that I think it's really important that we have these immunizations available for children, so I'll just add that to the group that also felt that way. And I think we're all using the same data to get to that point.

I think what we're missing here is some of the facts that any time we're going to consider any of the age groups -- so I do think there's probably not going to be too much of a difference between the next age group that's being considered, the 6- to 12-year-olds and the group that is already being immunized. And we'll have a lot of data to understand the risks of the adverse reactions. But we're not actually looking at

that.

So I think if we're going to consider these coming forward for anything, whether it's EUA and licensure -- and I do think that the length of follow up is not what's so important. Again, we're not going to see -- we're not seeing more adverse events later on. We're seeing them within this early time period. So I think that can be caught.

What we need to do is increase the number of our pediatric population within these so whatever 12- to 15-year-olds that we can capture. We're not capturing everyone and so expanding that. I know that's question three, but this is going to be important for this question as well as understanding risk factors.

So we have real -- lots of capability to get EHR data that we're not using. So I think that's really important. And it should come, I think personally, before a committee before this gets expanded out so that people can consider the data at hand at the time when these studies have been completed

and the request has gone into the FDA for any kind of expansion of use.

I do think that the zero -- or I'm sorry -- the six-month to two-year is a very different question. And the other thing that I haven't heard in the conversations yet is we really need to do a better job of understanding the dose escalation. We don't seem to take any pause there. They've been moved fairly quickly with the current doses, which is great.

But what we're seeing over and over is that the immune response in younger people is higher. It's not less inferior, of course. That's the only mark that we have to move forward. But it's actually higher, and that could be a marker of how we're looking at adverse events because a lot of these seem immune induced. And if children would do better with a lower dose, I think that's really important.

The other thing that isn't part of this conversation is we choose three weeks, four weeks, whatever it is. The interval also might be important for children. So I think we need to just take a pause

in the -- back up those preclinical studies in the phase 1 and 2 and really understand what we're doing before we move forward to phase 3. Then the numbers of 3,000 with a split in the vaccinated and unvaccinated is probably going to be fine because we'll never achieve higher numbers to get to an adverse event. And we're going have to do that in our post-licensure.

So if our post-licensure, then, could actually have increased enhancement for (A) the pediatric adverse events that we're looking for and, (B) a better population. Because it sounds like only 10 percent of the pediatric population is in the current systems.

With that said, I also think that, typically, we don't look mechanistically during these clinical trials, but there's no reason we can't lean on our studies to do some of that. There's no reason while we're drawing blood that we can't look for the signal that might be relevant to myocarditis.

So we know people are studying very clearly myocarditis associated with COVID. So you can actually look at those markers post-vaccine and try and come up

with some risk factors so that we can actually have a better idea when we're immunizing, who would be at risk for some of these adverse events and in addition that will have the epidemiologic studies. So that's all.

DR. ARNOLD MONTO: All right, thank you. Before we move on to the next discussion topic, I would like to know -- we've heard comments about the need to be able to roll out the vaccines if we start seeing more disease. How important is it, Dr. Gruber, Dr. Fink, for us to weigh in about emergency use versus licensure? We really haven't talked much about that. And then we're going on to the next discussion topic.

DR. DORAN FINK: I guess, Dr. Gruber and I came on simultaneously. Maybe she can add to my perspective. I guess it would be good to hear in more explicit terms -- I think we've heard from some people -- whether we should be contemplating Emergency Use Authorization for use in these younger age groups. And also, whether the duration of follow up that has supported Emergency Use Authorization for adults and in one instance, adolescents, would also be reasonable for

any of these younger age groups.

DR. ARNOLD MONTO: Well, we have a -- adolescents is our next question, our next discussion topic.

DR. DORAN FINK: That's for licensure, though.

DR. ARNOLD MONTO: Oh, that's for licensure. Yeah, but what you --

DR. MARION GRUBER: Yeah.

DR. ARNOLD MONTO: -- you mean -- so, for new applications?

DR. MARION GRUBER: Well, I don't want to really oppose what you just said. But to me, when I hear that these vaccines need to be ready in case we need it, then I think I'm hearing -- people who spoke in that regard I think by implication would have to be supportive of an EUA because a licensure just will take a bit longer. And so I don't know if we need explicit discussions on that at this point. If any of what I've heard is that people were comfortable about the duration of follow up that is being proposed here, and (phonetic) saying that extending the duration of follow

up probably doesn't really add much in terms of information to be gained, especially for rare adverse events.

I also seem to hear that regardless of the size of the database to support EUA or licensure, there is not a differentiation there, that we need a robust safety database in terms of the -- and regardless of whether EUA or licensure. And if I'm wrong with my understanding there, then I would like to be corrected, but that's what I've heard.

DR. ARNOLD MONTO: That's what I've heard as well. If there is anybody who disagrees with that summary, could you raise your hands now -- I know there are hands raised already -- because we really need to move on to the next topic. Dr. Kurilla, is your hand raised? I can't tell.

DR. MICHAEL KURILLA: Yes, it is, Arnold.

DR. ARNOLD MONTO: Okay.

DR. MICHAEL KURILLA: Yes, the comments I wanted to make was that while I'm in agreement with most of what has been discussed, I really don't see the

pursuit of EUA in this instance because of all of the studies that will need to be done in terms of dose ranging that will have to be performed. And so the timeframe with which all of this is going to take place doesn't seem to be aligned with both -- when we would think we would need to use an EUA under certain situations. I'm not really sure if we saw caseloads going up if that would automatically imply that, oh, we have to start vaccinating kids immediately.

And secondly, I don't really see this is an emergency in children. Now, having some sort of expanded access program or an EUA that's targeted towards children at high risk, I could see subgroups of children that really would need this vaccine. But I think for the broader general population -- yes, it has a public health impact -- but for the individual getting the vaccine for children who don't really see a lot of serious disease at all, very, very low risk, the EUA just seems overkill in my opinion.

DR. ARNOLD MONTO: Okay. That was the only comment from the group. Otherwise, I think we are more

or less in agreement with your summary. Let's go on, then, to question -- or topic number two, which has to do with the adolescents. "Provided there is sufficient evidence of effectiveness to support benefit of COVID-19 preventive vaccines for adolescents... discuss the safety data, including database size and duration of follow up, that would support licensure."

Note, only licensure, not Emergency Use Authorization. And I would assume this is -- since we've already got six months on the table, that this would be accepting the six months or requesting for longer or larger database size. So, Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Yes, thank you, Dr. Monto. When I looked at this question, the thing that came to my mind was actually to ask another question, which was where are we at with the licensure for adults? Because this is a question that I field all the time from family, friends, neighbors, people who write to me, members of the community. Because I think we would be a lot further along in our consideration and discussions around how many people we need in a

safety database for adolescents if we knew what the numbers look like for adults. So that's one point I'd like to make. And I don't know if anybody from the FDA is prepared to answer that question.

But with regard to the size of the database and the duration of follow up, the specific question that's asked here, again, for licensure, obviously I think that the safety database has to be robust. I'm not certain of what the actual number needs to be. I'm not sure how people are actually coming up with numbers. I can't do that other than simply guessing.

And the duration of follow up, there I think we do have an obligation to have it be at least six months and perhaps up to a year in order to really have robust data that we can rely on. I'll stop there.

DR. ARNOLD MONTO: Dr. Gans.

DR. HAYLEY GANS: Sorry, did you call on me?

DR. ARNOLD MONTO: Your hand was raised.

DR. HAYLEY GANS: Oh, yeah, thank you. I didn't hear Gans. I heard Pans. Anyway, yeah, thank you. I don't think that this age --

DR. ARNOLD MONTO: I do my best.

DR. HAYLEY GANS: I think that this age group is probably the easiest age group. And I think we probably have, after all the doses that have been given, quite a bit of data now to start supporting the safety.

The real question that is still in everyone's mind is the myocarditis. So I think until that safety datapoint or signal is actually worked out -- and we heard a lot of questions regarding that without a lot of answers today. So I think that rather than the duration, I think because this is a unique situation where we have a ton of already post-use information that we don't usually have when vaccines come up for licensure, that this is a unique opportunity to have more data rather than time. I think time is not of the essence. So I think in order to get to licensure we need enhanced information on the current safety signals that we're already seeing.

DR. ARNOLD MONTO: I don't see, miraculously, any other hands raised. Anybody not comfortable with

the six-month time? Are we being asked whether it should be any shorter than that? I don't believe that's the case unless -- and somebody from FDA would like to mention it? So we seem to be comfortable as a group with the six-month follow up that was in the original guidance document. That was easy.

Let's go on to discussion question number three, which is pretty well open ended and I think may be as important as some of our discussions in item one and related to item number one. "Please discuss studies following licensure and/or issuance of an EUA to further evaluate safety and effectiveness of COVID-19 vaccines in different pediatric age groups," pretty much an open-ended question. And we can, I guess, talk about not only statistics but pathogenesis of side effects and things like that. So, Dr. Chatterjee.

DR. ARCHANA CHATTERJEE: Thanks, Dr. Monto. With regard to this question, one of the points I wanted to make earlier -- or I'd like to bring it up now -- is with regard to racial and ethnic minorities and making sure that a sufficient proportion of

children from these different groups are included in addition to the different age groups.

Because it's certainly possible -- and we've seen that with regard to the pandemic itself, with the disease itself, that the disease seems to affect different racial and ethnic minorities in different ways. So to ensure that any post-licensure or post-EUA studies that are done include a sufficient number of children from minoritized background, I think that would be an important aspect to keep in mind.

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

DR. STEVEN PERGAM: Thanks, Arnold. Yeah, I sort of echo Dr. Chatterjee's earlier comment about licensure for the adult vaccine, which I'm still unclear when we're going to be reviewing the BLAs for those. I think what'll be really important in these future studies is once we have additional data about immunogenicity endpoints in the adult trials, which I know are ongoing, we have to make sure that we're looking at these more specifically in the pediatric populations. Specifically, T cell immunity is going to

be important beyond just the antibody levels.

And I'm really curious, specifically, with the different vaccines. I know you didn't want us to bring up the different vaccines between Pfizer and Moderna. But Pfizer and Moderna do have different dosage levels, and they'd be really -- I'm curious about what Dr. Kurilla had brought up is I'm looking at these immunogenicity levels with the different dosing strategies that they're going to be putting forward. So I think that'll be a really important piece as we look at efficacy within the trials and then, obviously, that'll plan to safety as well.

DR. ARNOLD MONTO: Thank you. And Dr. McInnis.

DR. PAMELA McINNES: Thank you, Arnold. So I think there's the age-old issue of waning immunity and being able to understand the kinetics of this response. This is not unique to pediatric groups but will apply to adults as well. So I think that's sort of a no brainer of what has to be followed for ongoing effectiveness of these vaccines. And, in fact, then

perhaps we will get better at understanding what might actually be a marker of immunity, and we'll learn more about what's happening with functional antibody. So I think that's really important.

I think the safety piece is that I'm not convinced that this has to be newly invented. We've obviously got wonderful systems in place. And, hopefully, participants in studies are going to be able to be followed up long-term and that we will hopefully be able to pick up medically attended illnesses and hospitalizations, et cetera, and understand more about that post-licensure. Thank you.

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

DR. MARK SAWYER: Hi, it (audio skip) without saying, but given the unusual immunologic responses in general that we're seeing in children, we need to be vigilant for vaccine enhanced disease that like we see in Dengue with vaccination in naïve people who subsequently then get infected. So I want to keep that on the radar along with the other previous comments

about expanding the breadth of immunologic phenomenon that we look for after vaccine.

And then I think because we've all discussed at fair length here how -- the concern about myocarditis and other side effects which seem to generally be worse after the second dose, I think we need some studies on single dose and whether that might be adequate going forward.

DR. ARNOLD MONTO: Dr. Kurilla.

DR. MICHAEL KURILLA: Thank you, Arnold. Yeah, so I agree with a lot of the comments that have been made, particularly about really doing some better detailed understanding of the immunological response.

Early on in this outbreak there was a lot of talk about a little bit of cross reactivity that some people experienced with prior coronavirus infection. That may be -- that may end up be -- influencing some of the vaccine response and also some of the adverse events that we're seeing in children. Or the younger the children are, the more unique they are going to be in terms of being more coronavirus naïve to begin with.

So that may actually have an impact on their long-term response to coronaviruses in general.

I think the myocarditis is something that needs to be looked at closely because we're likely seeing the tip of the iceberg, and there may be subclinical aspects to that. And that may be more important developmentally in terms of children that may have some long-term impacts, much more subtle, but may lead to long-term events while they're adults.

So I think those two things that we have to pay a little more attention to and be prepared to follow up because we're likely to find some surprises going forward. Thank you.

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

DR. HAYLEY GANS: (Audio skip) -- points that have been raised which I think are great. Along the lines of what Dr. Sawyer was saying in terms of the enhanced disease that may be seen and it may have a preference for people who are more immune response, so kids, I do think we need to continue to look at breakthrough disease.

So while it may that the hospitalization rates and other rates are down, I do think we still need to understand the epidemiology of how people get sick, especially when we come maybe potentially into a second season and what is going to be circulating. We don't know. So I think that's going to be an important follow up study that needs to be added to the ones that have already been stated and has been stated by Dr. Chatterjee.

I think we do need to look because these will be given particularly to young children with their other vaccines. So we have to look at if there's any interference, not necessarily with safety as was already raised for the fever, but also the immune response. And then I can't iterate enough, because I've said it several times, the immune response really needs to be well adjusted.

And then I do think that the way that we use vaccines in children is usually a prime boost type of strategy. So I do think that including (phonetic) a second dose is going to be necessary. So even though

the recommendation was to look at single dose and that's fine, I do think we also need to do studies, again as I said, with different intervals because I do think that initial immune response is likely to need a prime boost feature to it. And we just need to get it right on dose and timing.

DR. ARNOLD MONTO: Dr. Meissner.

DR. CODY MEISSNER: Thank you, Arnold. And I think that -- I agree with what Ofer Levy said early on and I think what everyone else is saying. If we had more information about what's going on with myocarditis, it would be much easier to address some of these safety questions for younger children because we're really operating somewhat in the blind here. And so I agree with what I think several people are saying because there are a number of options.

We could have a longer interval for the first dose and the second dose. We could reduce the amount of mRNA in the vaccines. Or, as has been suggested initially, we may not even need to give a second dose to children because this is a pretty -- it stimulates a

pretty aggressive response. But I think these are all issues that need to be addressed, hopefully, before it's necessary to use these vaccines in high numbers in young children.

And we haven't thought about the other possibility. Maybe the numbers, the amount of disease are going to continue to decline. What happens if the slope of the number of new cases goes down? It seems to me that's more likely than it will go up. And so these are going to be even more difficult questions to answer in terms of balancing risk and benefit. Over.

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

DR. MICHAEL NELSON: Thank you. I just wanted to comment on the changes in the schedule and, obviously, with the dose and to be very careful that we would not do this passively post-licensure, in fact, that they should be controlled studies if pursued. Since we're using immunobridging technique, I would think the same prime boost schedule would need to be followed in order to provide the reassurance of safety beyond expanding the use afterwards.

I also do want to focus a little bit on dose and think about, again, how important it is to discriminate what the right dose is for the right child and also look at the immune response of children. It may not be exactly the same qualitatively with respect to the antibodies that are generated. So if we're hanging our hat on neutralizing antibodies, we need to characterize that immune response in various age groups as well as the neutralizing effect against the multiple variants that are emerging.

And I want to go back briefly to MIS-C as well. I noted in the two trials in ClinicalTrials.gov that one of the two vaccines excluded it from enrollment, one didn't. I do think we need to track this population specifically in their response to any doses of the vaccines as we follow them. And we need more information as well on the immunosuppressed and clearly, our ethnicity, diversity with respect to immune response and safety. Thank you.

DR. ARNOLD MONTO: Thank you. And finally, Dr. Chatterjee who is going to have the last word.

DR. ARCHANA CHATTERJEE: Thank you, Dr. Monto. I know we had decided we are not going to talk about variants, but I think this question actually deserves just a brief mention that if we talk about effectiveness post-licensure or authorization, as the variants continue to evolve and appear in our population, I think this would be a critical piece as well to look at to see if the current vaccines are actually serving us or if these variants are escaping our current vaccines.

DR. ARNOLD MONTO: Thank you. I think we are all aware that that's a key issue, looking. And many individuals and groups are now looking at escape related to variants.

When we went into this discussion topic, the series of discussion topics, I said that it would be very difficult to summarize. And I do think it is surprisingly easier to summarize for number two, discussion topic two, where I think there was a reasonable support for about the same kind of duration to full licensure was in the original documents for the

adult vaccines. Clearly, we had a difference -- a great deal of emphasis on post-licensure evaluation to go along with some of the issues related to question one.

I think we heard more agreement with the proposed numbers and duration that was in the briefing document than disagreement. We had only a few people who really disagreed with some of the approaches. We heard that the numbers will certainly have to be larger for the youngest age groups.

We really did not have any kind of unanimity about emergency use versus licensure. We heard some who wanted to have the vaccine available if you needed it but others who felt that we ought to go to full -- not have an Emergency Use Authorization, particularly in younger individuals. So it's very difficult to summarize about our views, our opinions in that regard. But to my surprise, and happy surprise, I think we heard much more agreement than disagreement about all of the points related to discussion topic one.

So thank you, and I'd like to hand over to Dr.

Marks who I believe has some concluding comments.

DR. PETER MARKS: So Dr. Monto and Committee members, I just want to take a moment to thank everyone for their participation today. I think it's very important to have the type of dialogue that took place. I think this is clearly an area where achieving consensus, as people can see, may be a little bit challenging. But it's very important that we have the dialog, and I'm very, very grateful for everyone's time today.

I, first of all, want to thank the Advisory Committee staff that has done an incredibly great job putting this together at FDA. I want to thank our Office of Vaccines, Office of Biostatistics and Epidemiology who put things together. I also want to thank all of you on the Committee for a very frank discussion. I think all of your perspectives are very important as we put things together.

I also want to take a moment to remember all the children who have died of COVID-19 in this pandemic because that should not be forgotten here. I just need

to reiterate something that this is an illness that takes the lives of children. We know that over 300 children have died in the pandemic so far and that if one looked at the death rate of the 11- to 17-year-olds who had COVID-19, it was about 1 in 3,600 of those individuals. And since we had over 1 million cases in that age range, you can see that there are deaths due to this. So I want to remember those.

And as we go forward, I think all of us have as a goal to eliminate any vaccine preventable deaths that we can with a reasonable benefit-risk. So as we leave today, I really want to thank you for all of the thoughts about this because I think everyone is obviously trying to do their best to achieve that goal. And I appreciate all the different viewpoints.

Thanks also to everyone who tuned in today to listen to this webcast. And I'll turn it back over to Dr. Monto or Dr. Atreya.

DR. ARNOLD MONTO: I think we turn it over to Dr. Atreya now to formally close the meeting.

MEETING ADJOURNED

DR. PRABHAKARA ATREYA: Okay. Great. Thank you, all. Thank you, Dr. Arnold Monto, and the entire VRBPAC team and then all the staff who participated. These are great discussions and then a great meeting all around. Thank you and I formally close the meeting now. So the meeting will adjourn now. Okay. Thank you and have a good evening. Bye-bye.

[MEETING ADJOURNED]