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Center for Biologics Evaluation and Research (CBER)

Division of Scientific Advisors and Consultants

188th Meeting of the Vaccines and Related Biological Products Advisory Committee (VRBPAC)

Zoom Video Conference

(Open Session)

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Chair

Hana El Sahly, MD	Professor, Department of Molecular Virology and Microbiology and Medicine, Baylor College of Medicine	Houston, TX

Members

Adam C. Berger, PhD	Director, Division of Clinical and Healthcare Research Policy, Office of Science Policy, Office of the Director, National Institutes of Health	Bethesda, MD
Henry H. Bernstein, DO, MHCM, FAAP	Professor of Pediatrics, Zucker School of Medicine at Hofstra/Northwell, Department of Pediatrics, Cohen Children's Medical Center	New Hyde Park, NY
Archana Chatterjee, MD, PhD (Topic II Only)	Dean, Chicago Medical School, Vice President for Medical Affairs, Rosalind Franklin University of Medicine and Science	North Chicago, IL
Hayley Gans, MD	Clinical Professor, Pediatrics-Infectious Diseases, Stanford Medicine Children's Health	Stanford, CA
Holly Janes, PhD	Professor, Vaccine and Infectious Disease Division, Public Health Sciences Division, Fred Hutchinson Cancer Center	Seattle, WA
CAPT Sarah Meyer, MD, MPH	Chief Medical Officer, Immunization Services Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention	Atlanta, GA
Arnold S. Monto, MD	Thomas Francis Jr. Collegiate Professor, Emeritus of Public Health, Professor Emeritus of Epidemiology, School of Public Health, University of Michigan	Ann Arbor, MI
Michael R. Nelson, MD, PhD	Chief, Asthma, Allergy, and Immunology Division, UVA Health & UVA School of Medicine	Charlottesville, VA
Paul Offit, MD	Director, Vaccine Education Center, Professor of Pediatrics, Division of Infectious Diseases, Children's Hospital of Philadelphia, Maurice R. Hilleman Professor of Vaccinology, Perelman School of Medicine, University of Pennsylvania	Philadelphia, PA
Stanley Perlman, MD, PhD	Professor, University of Iowa Distinguished Chair, Departments of Microbiology and Immunology, Carver College of Medicine, University of Iowa	Iowa City, IA

Andrea Shane, MD, MPH, MSc (Topic II Only)	Professor of Pediatrics, Division of Infectious Disease, Marcus Professor of Hospital Epidemiology and Infection Prevention, Emory University School of Medicine	Atlanta, GA

Temporary Voting Members

Karen Kotloff, MD (Topic I Only)	John A. Scholl, MD and Mary Louise School, MD, Distinguished Professor, Associate Director, Clinical Research, Center for Vaccine Development and Global Health, University of Maryland School of Medicine	Baltimore, MD
Sarah Long, MD (Topic I Only)	Emeritus Chief, Infectious Diseases, Section of Infectious Diseases, St. Christopher's Hospital for Children, Professor of Pediatrics, Drexel University College of Medicine	Philadelphia, PA
Allison Malloy, MD, MSc (Topic I Only)	Associate Professor, Department of Pediatrics, Infectious Disease Faculty, F. Edward Herbert School of Medicine, Uniformed Services University of Health Sciences (USUHS)	Bethesda, MD
Tracy Ruckwardt, PhD (Topic I Only)	Staff Scientist and Chief of the Respiratory, Viruses Core at VRC, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH)	Bethesda, MD

Alternate Industry Representative

Robert S. Janssen, MD	Chief Medical Officer and Senior Vice President, Clinical Development, Dynavax Technologies Corporation	Emeryville, CA

Consumer Representative

Jay M. Portnoy, MD	Professor of Pediatrics, University of Missouri – Kansas City, School of Medicine, Director, Division of Allergy, Asthma, and Immunology, Children's Mercy Hospitals and Clinics	Kansas City, MO

Speakers and Guest Speakers

Fatimah Dawood, MD (Speaker, Topic I)	Team Lead, Epidemiology and Vaccine Assessment Team, Coronavirus and Other Respiratory Virus Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC)	Atlanta, GA
Pedro A. Piedra, M.D. (Guest Speaker, Topic I)	Professor, Department of Molecular Virology and Microbiology and Pediatrics, Director, Pandemic Threat Technology Center, Director, Respiratory Virus Diagnostic Laboratory, Baylor College of Medicine	Houston, TX
Christine Shaw, PhD (Industry Speaker, Topic I)	Vice President, Portfolio Head, Infectious Disease Vaccines, ModernaTX, Inc.	Cambridge, MA
Matthew Snape, MBBS, MD, FRCPCH, FMedSci, MBE (Industry Speaker, Topic I)	Vice President, Clinical Development, Infectious Diseases, Pediatric and Maternal Vaccines, Moderna Biotech Distributor UK Limited, Harwell Science and Innovation Campus	United Kingdom

FDA CBER Participants

Peter Marks, MD, PhD	Director, Center for Biologics Evaluation & Research, Food and Drug Administration	Silver Spring, MD
Celia Witten, PhD, MD	Deputy Director, Center for Biologics Evaluation & Research, Food and Drug Administration	Silver Spring, MD
Karen Elkins, PhD (Speaker, Topic II)	Associate Director for Science, Office of the Director, Center for Biologics Evaluation & Research, Food and Drug Administration	Silver Spring, MD
David C. Kaslow, MD (Speaker, Topic I)	Director, Office of Vaccines Research & Review, Center for Biologics Evaluation & Research, Food and Drug Administration	Silver Spring, MD
Karin Bok, M.S., PhD	Deputy Director, Office of Vaccines Research & Review, Center for Biologics Evaluation & Research, Food and Drug Administration	Silver Spring, MD
Sudhakar Agnihothram, BPharm, PhD	Associate Director of Office Regulatory Initiatives, Office of Vaccines Research & Review, Center for Biologics Evaluation & Research, Food and Drug Administration	Silver Spring, MD
Tod Merkel, PhD (Speaker, Topic II)	Associate Director for Research, Office of Vaccines Research & Review, Center for Biologics Evaluation & Research, Food and Drug Administration	Silver Spring, MD

Rebecca Reindel, MD	Director, Division of Clinical and Toxicology Review, Office of Vaccines Research & Review, Center for Biological Evaluation & Research, Food and Drug Administration	Silver Spring, MD
Hana Golding, PhD (Speaker, Topic II)	Chief and Principal Investigator, Laboratory of Retroviruses (LR), Division of Viral Products, Office of Vaccines Research & Review, Center for Biologics Evaluation and Research, Food and Drug Administration	Silver Spring, MD
Carol Weiss, MD, PhD (Speaker, Topic II)	Chief and Principal Investigator, Laboratory of Immunoregulation (LI), Division of Viral Products, Office of Vaccines Research & Review, Center for Biologics Evaluation & Research, Food and Drug Administration	Silver Spring, MD
Mark Connelly, MD (Speaker, Topic I)	Team Leader, Clinical Review Branch 3, Division of Clinical and Toxicology Review, Office of Vaccines Research & Review, Center for Biologics Evaluation & Research, Food and Drug Administration	Silver Spring, MD
Designated Federal Officer		
Sussan Paydar, PhD	Division of Scientific Advisors & Consultants, Center for Biologics Evaluation & Research, Food and Drug Administration	Silver Spring, MD
Alternate Designated Federal Officer		
Kathleen Hayes, MPH	Division of Scientific Advisors & Consultants, Center for Biologics Evaluation & Research, Food and Drug Administration	Silver Spring, MD
Director		
Prabhakara Atreya, PhD	Division of Scientific Advisors & Consultants, Center for Biologics Evaluation & Research, Food and Drug Administration	Silver Spring, MD
Committee Management Officer		
Joanne Lipkind, MS	Division of Scientific Advisors & Consultants, Center for Biologics Evaluation & Research, Food and Drug Administration	Silver Spring, MD
Committee Management Specialist		
Lisa Johnson	Division of Scientific Advisors & Consultants, Center for Biologics Evaluation & Research, Food and Drug Administration	Silver Spring, MD

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Opening Remarks: Call to Order and Welcome

Dr. El Sahly: Good morning, everyone, and welcome to the 188th meeting of the Vaccines and Related Biological Products Advisory Committee meeting to the FDA Center for Biologics Evaluation and Research. We will begin the day with Topic I. Topic I will be a discussion of the considerations for RSV vaccine safety in pediatric populations. To kick off the meeting, I would like to invite Dr. Sussan Paydar. Dr. Sussan Paydar will give us some administrative announcements pertaining to the meeting. Dr. Paydar

Administrative Announcements

Dr. Paydar: Thank you, Dr. El Sahly. Good morning, everyone. This is Sussan Paydar, and it is my great honor to serve as the Designated Federal Officer for today's 188th Vaccines and Related Biological Products Advisory Committee meeting. On behalf of the FDA, the Center for Biologics Evaluation and Research, CBER, and the Committee, I'm happy to welcome everyone for today's virtual meeting. Today the Committee will meet in open session to discuss considerations for Respiratory Syncytial Virus, RSV, vaccine safety in pediatric populations. We'll also hear overviews of the Laboratory of Immunoregulation and Laboratory of Retroviruses Research Programs in the Division of Viral Products, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research. Today's meeting and the topics were announced in the Federal Register Notice that was published on October 24, 2024. Next slide, please.

At this time, I would like to acknowledge outstanding leadership of Dr. Peter Marks, Director of Center for Biologics Evaluation and Research; Dr. David Kaslow, Director of Office of Vaccines Research and Review; Dr. Karin Bok, Deputy Director,

Office of Vaccines Research and Review; Dr. Sudhakar Agnihothram, Associate Director of Office Regulatory Initiatives, OVRR; and Dr. Rebecca Reindel, Director of Division of Clinical and Toxicology Review, OVRR. Next slide, please.

I also would like to thank my Division Director, Dr. Prabhakara Atreya, for her excellent leadership, and my team, whose contributions have been critical for preparing today's meeting: Ms. Kathleen Hayes, Ms. Joanne Lipkind, and Ms. Lisa Johnson. Next slide, please. I also would like to express our sincere appreciation to AV team, Mr. Derek Bonner, Mr. Corey Farley and Mr. Deon Wrenn, in facilitating the meeting today. Also, our sincere gratitude goes to many CBER and FDA staff working very hard behind the scenes trying to ensure that today's virtual meeting will also be a successful one like all the previous VRBPAC meetings. Please direct any press media questions for today's meeting to FDA's Office of the Media Affairs at FDAOMA@fda.hhs.gov. The transcriptionists for today's meeting are Myra Angulo and Virginia Diaz from Andean Consulting Solutions International. We'll begin today's meeting by taking a formal roll call for the Committee Members and Temporary Voting Members. When it is your turn, please turn on your video camera, unmute your phone, and then state your first and last name, institution, and areas of expertise. And when finished, you can turn your camera off, so we can proceed to the next person. Please see the member roster slides in which we'll begin with the Chair, Dr. Hana El Sahly.

Roll Call and Introduction of Committee

Dr. El Sahly: Good morning, everyone. My name is Hana El Sahly. I'm an adult ID physician at Baylor College of Medicine and my research focus is clinical vaccine development.

Dr. Paydar: Great. Thank you. Next is Dr. Adam Berger.

Dr. Berger: Hi, my name is Adam Berger. I'm the Director of the Division of Clinical and Healthcare Research Policy at the National Institutes of Health. My background-- I'm a geneticist with additional training in immunology. Thank you.

Dr. Paydar: Thank you. Dr. Henry Bernstein.

Dr. Bernstein: Good morning, everyone. My name is Hank Bernstein. I'm a Professor of Pediatrics at the Zucker School of Medicine at Hofstra/Northwell. My areas of special interest are vaccinology, including vaccination delivery. Thank you.

Dr. Paydar: Thank you. Dr. Archana Chatterjee, she will join us for Topic II, so please, next slide, please. Dr. Holly-- Hayley Gans.

Dr. Gans: Good morning. I'm Dr. Hayley Gans. I'm a Professor of Pediatrics and Pediatric Infectious Disease at Stanford, and my area of research is host pathogen interface, including immune responses to vaccine. Thank you.

Dr. Paydar: Thank you. Dr. Holly Janes.

Dr. Janes: Good morning. I'm Holly Janes. I'm a Biostatistician by training. I am at the Fred Hutchinson Cancer Research Center in Seattle and my specialty is in vaccine evaluation.

Dr. Paydar: Great. Thank you. Dr. Robert Janssen, our Alternate Industry Representative. Dr. Janssen.

Dr. Janssen: I'm Dr. Robert Janssen. I'm Chief Medical Officer at Dynavax Technologies and my area of interest is clinical vaccine research.

Dr. Paydar: CAPT Sarah Meyer. Next slide.

CAPT Meyer: Morning. My name is Sarah Meyer. I'm a Pediatrician and I serve as the Director of the Immunization Safety Office at the CDC.

Dr. Paydar: Thank you. Dr. Arnold Monto.

Dr. Monto: I'm Arnold Monto. I'm at the University of Michigan School of Public Health, where I have been studying respiratory infections, particularly in the community, their occurrence and prevention. Thank you.

Dr. Paydar: Thank you, Dr. Monto. Dr. Michael Nelson.

Dr. Nelson: Hi, I'm Michael Nelson, Chief of the Asthma, Allergy, and Immunology Division at the University of Virginia. I'm a trained allergist and immunologist, and my area of expertise is vaccine adverse events. Thank you.

Dr. Paydar: Great. Thank you. Dr. Stanley Perlman. Actually-- I'm so sorry. Dr. Paul Offit. I jumped him.

Dr. Offit: Good morning, Sussan. I'm Paul Offit from the Division of Infectious Diseases and the Professor of Pediatrics at the Children's Hospital of Philadelphia and the University of Pennsylvania School of Medicine. My interest is in mucosal vaccines and vaccine safety. Thank you.

Dr. Paydar: Thank you, Dr. Offit. Next is Dr. Stanley Perlman.

Dr. Pergam: Hi, I am Stanley Perlman. I'm a Pediatric Infectious Diseases Specialist and a Professor of the Department of Microbiology and Immunology at the University of Iowa, and my expertise is in coronaviruses.

Dr. Paydar: Thank you. Dr. Jay Portnoy, our Consumer Representative.

Dr. Portnoy: Good morning. I'm Dr. Jay Portnoy. I'm a Professor of Pediatrics at the University of Missouri – Kansas City School of Medicine. I'm an allergist immunologist at Children's Mercy Hospital in Kansas City.

Dr. Paydar: Great. Thank you. Dr. Andrea Shane, she will also join us for Topic II. Next we'll do a roll call of our Temporary Voting Members for Topic I. We'll start with Dr. Karen Kotloff.

Dr. Kotloff: Hi, I'm Karen Kotloff. I'm a Professor of Pediatrics and Pediatric Infectious Disease at the University of Maryland School of Medicine, Center for Vaccine Development and Global Health. My interest is in clinical vaccine development and the epidemiology of infectious diseases in the U.S. and in developing countries.

Dr. Paydar: Great. Thank you. Dr. Sarah Long.

Dr. Long: Good morning. I am Sarah Long. I'm a Professor of Pediatrics and Pediatric Infectious Diseases at Drexel University College of Medicine and a recent member of CDC's ACIP, where I chaired the work group on maternal infant vaccine and monoclonal antibody to protect infants from RSV.

Dr. Paydar: Thank you. Dr. Allison Malloy.

Dr. Malloy: Hi, my name is Allison. I'm a Pediatric Infectious Disease Specialist and I work at the Uniformed Services University of Health Sciences and our research focuses on respiratory viruses and mucosal immunology. Thanks.

Dr. Paydar: Great. Thank you. Dr. Tracy Ruckwardt.

Dr. Ruckwardt: Good morning. My name is Tracy Ruckwardt. I'm a staff scientist and Head of the Respiratory Viruses Core at the Vaccine Research Center in

NIAID at NIH. I've been studying RSV for more than 20 years, including work on age-dependent differences in adaptive immune responses and evaluation of immunity following preF vaccination in humans. Thank you.

Dr. Paydar: Great. Thank you so much. Thanks, everyone. For Topic I, we have a total of 16 participants: 15 voting and one non-voting member. Now I'll proceed with reading the FDA Conflict of Interest Disclosure Statement for the public record.

Conflict of Interest Statement

The Food and Drug Administration, FDA, is convening virtually today, December 12, 2024, for the 188th meeting of the Vaccines and Related Biological Products Advisory Committee, VRBPAC, under the authority of the Federal Advisory Committee Act, FACA, of 1972. Dr. Hana El Sahly is serving as the Voting Chair for today's meeting. Today on December 12, 2024, under Topic I, the Committee will meet in open session to discuss considerations for Respiratory Syncytial Virus, RSV, vaccine safety in pediatric populations. This topic is determined to be a Particular Matter of General Applicability, PMGA. With the exception of the Industry Representative Member, all Standing and Temporary Voting Members of the VRBPAC are appointed Special Government Employees, SGEs, or Regular Government Employees, RGEs, from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this Committee's compliance with federal ethics and conflict of interest laws, including but not limited to 18 U.S.C., Section 208, is being provided to participants in today's meeting and to the public. Related to the discussions at this meeting, all members RGE and SGE consultants of this Committee have been screened for potential financial conflict 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, teaching, speaking, writing, patents and royalties, and primary employment. These may include interests that are occurring or under negotiation. FDA has determined that all members of this Advisory Committee, both regular and temporary members, are in compliance with federal ethics and conflict of interest laws.

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

Based on today's agenda and all financial interests reported by Committee members and consultants, there have been no conflict-of-interest waivers issued under 18 U.S. Code 208, in connection with this meeting.

We have the following consultants serving as Temporary Voting Members. Dr. Karen Kotloff, Dr. Sarah Long, Dr. Allison Malloy and Dr. Tracy Ruckwardt. Dr. Robert Janssen of Dynavax will serve as the Alternate Industry Representative for today's meeting. Industry representatives are not appointed as Special Government Employees and serve as Non-Voting Members of the Committee. Industry Representatives act on behalf of all regulated industry and bring general industry perspective to the Committee. Dr. Jay Portnoy is serving as the Consumer

Representative for this Committee. Consumer representatives are appointed Special Government Employees and are screened and cleared prior to their participation in the meeting. They are Voting Members of the Committee.

We have several federal and non-federal guest speakers as well as industry guest speakers today making various presentations on timely and relevant topics. The following speakers and guest speakers were invited for this meeting. Dr. Fatima Dawood, Team Lead Epidemiology and Vaccine Assessment Team, Coronavirus and Other Respiratory Virus Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; Dr. Pedro Piedra, Professor, Department of Molecular Virology and Microbiology and Pediatrics, Director, Pandemic Threat Technology Center, Director, Respiratory Virus Diagnostic Laboratory, Baylor College of Medicine, Houston, Texas; Dr. Christine Shaw, Vice President, Portfolio Head, Infectious Disease Vaccines, Moderna; Dr. Matthew Snape, Vice President Clinical Development, Infectious Diseases, Pediatric and Maternal Vaccines, Moderna.

Disclosure of conflicts of interest for speakers, guest speakers and responders follow applicable federal laws, regulations, and FDA guidance. FDA encourages all meeting participants, including Open Public Hearing speakers, to advise the Committee of any financial relationships that they may have with any affected firms, its products and, if known, its direct competitors. We would like to remind Standing and Temporary Members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to inform the DFO and exclude themselves from the discussion, and their exclusion will be noted for the record. This concludes my reading of the Conflict

of Interest Statement for the public record. At this time, I would like to hand over the meeting to our chair, Dr. Hana El Sahly. Thank you.

Dr. El Sahly: Great. Thank you, Sussan. I would like to invite now Dr. David Kaslow. Dr. David Kaslow is the Director of the Office of Vaccine Research and Review, OVRR, at the FDA. Dr. Kaslow will introduce Topic I to the Committee and the public. Dr. Kaslow.

Overview of Topic I

Dr. Kaslow: Great. Thank you, Dr. El Sahly. And on behalf of the Office of Vaccines Research and Review, let me welcome all to this 188th VRBPAC convening. We're asking the Advisory Committee to consider two topics. Next slide, please. For Topic I, we're asking VRBPAC to discuss considerations for evaluating RSV vaccine candidates in infants and children, specifically in light of recent observations of clinically significant severe to very severe RSV lower respiratory tract infections following administration of investigational RSV vaccines in infants. We're also asking VRBPAC to consider two research programs. One in the Laboratory of Immunoregulation, the other in the Laboratory of Retroviruses, both in the Division of Viral Products. More on that topic later this afternoon. Next slide. Thank you.

A bit of context for Topic I. As discussed at the 2017 VRBPAC meeting, the observation of enhanced respiratory disease in studies of formalin-inactivated RSV vaccines conducted in the 1960s cast a decades-long shadow over RSV vaccine development. However, recent advances, including in various vaccine technologies, structural immunology and plausible mechanisms to explain vaccine-associated enhanced respiratory disease, have facilitated RSV vaccine development and evaluation in adults and in pregnant individuals and in pediatric populations. More recently,

approval of a long-acting RSV monoclonal antibody and a vaccine for maternal immunization, each of which provide passive RSV immunity during infancy, have partially addressed the unmet need for pediatric RSV vaccines. With that current context in mind, we asked VRBPAC to now consider two recent observations. First, five cases of severe to very severe RSV lower respiratory tract disease following administration of mRNA-based RSV vaccine candidates to presumed RSV-naïve infants, noting that the cause and mechanism of this observation have yet to be established. And second, a potential RSV monoclonal antibody RSV vaccine interaction observed after a first dose of RSV vaccine that may impact active immunization in infants and toddlers who are administered RSV vaccines after receiving long-acting RSV monoclonal antibodies. Next slide, please.

With that context and those new considerations in mind, and to frame the VRBPAC discussion on Topic I, we have asked our CDC colleague, Dr. Dawood, to review the epidemiology of RSV in U.S. children, and Dr. Piedra from the Baylor College of Medicine to cover clinical and nonclinical aspects of RSV vaccine safety in young children. We have then asked, and Moderna kindly agreed, to review nonclinical and clinical findings of their investigational RSV and RSV plus human metapneumovirus mRNA vaccines with a focus on infants and children less than two years of age. That will be followed by an FDA presentation by Dr. Connelly. After an additional Question and Answer Period and a brief lunch break, VRBPAC will go into Open Public Hearing Session with four speakers, including two sponsors of RSV vaccine candidates. As always, during the Open Public Hearing Session, the Chair or Committee Member may question a person concerning the scientific content of that person's presentation. Thereafter, 120 minutes have been allotted for VRBPAC to consider two discussion topics. Next slide, please.

First in follow-up to the 2017 VRBPAC, we are asking VRBPAC to have another focused discussion on RSV vaccine safety in pediatric populations based on the currently available evidence, namely the imbalance in severe RSV cases and available immunological data following mRNA RSV vaccination, and whether that evidence indicates a potential safety concern more broadly applicable to the evaluation of RSV vaccines in infants and toddlers, specifically the applicability to the broad range of other vaccine technologies and different antigenic confirmations in development. Then, based on that discussion, we are then asking VRBPAC to discuss whether the current nonclinical and clinical safeguards are sufficient and/or whether any additional nonclinical and clinical information should be considered and/or precautions should be taken when evaluating RSV vaccine candidates in infants and toddlers. Next slide, please.

Second, we're asking VRBPAC to discuss whether the preliminary immunogenicity data after a single dose of RSV vaccine in individuals who had previously received nirsevimab suggest a potential monoclonal vaccine interaction that may affect active immunization in infants and toddlers. And if so, whether any additional factors and data should be considered when evaluating sequential administration of RSV monoclonal antibodies followed by RSV vaccines in infants and toddlers, including potential impact on safety and/or effectiveness of subsequent parentally or mucosally administered RSV vaccines. Next slide, please.

Finally, I would like to draw VRBPAC's attention to this slide, which is slide 26, and Dr. Connelly's FDA presentation. I won't go through the seven items listed on this slide. Rather I wanted to note that first, these are potential considerations if the Committee determines that recent observations warrant for the recommendations beyond those made at the 2017 VRBPAC meeting. Second, and I want to be clear about

this, none of the RSV vaccine candidates based on live-attenuated RSV vectors are currently on clinical hold. And third, this list is not meant to be exhaustive, but rather to be representative of the topics we seek VRBPAC's advice today. I suggest this slide might be helpful as you listen to this morning's presentations and discuss any recommendations on today's Topic I. Next slide, please.

So let me conclude by again welcoming all; by thanking the VRBPAC members, including our four Topic I Temporary Voting Members, for your time preparing for and participating in today's VRBPAC Topic I; by thanking all of today's speakers, both invited and those in the Open Public Hearing Session; by thanking my colleagues here at FDA, who helped prepare for and organize this meeting on very short notice; and by thanking those of you who have joined this Open Public Meeting virtually. We do look forward to another productive VRBPAC meeting today. And with that, back to you, Dr. El Sahly.

Dr. El Sahly: Thank you so much, Dr. Kaslow, for this informative introduction. So, as Dr. Kaslow indicated, we have a rather involved task on hand today and I foresee a very engaging discussion. And to kick us off, Dr. Fatimah Dawood, Team Lead, Epidemiology and Vaccine Assessment Team, Coronavirus and Other Respiratory Viruses Division, National Center for Immunization and Respiratory Diseases at the CDC, will give us an overview of RSV epidemiology in U.S. children. Dr. Dawood.

RSV Epidemiology

Epidemiology of Respiratory Syncytial Virus in U.S. Children

Dr. Dawood: Thank you. Good morning. Next slide, please. During this talk we will review RSV disease burden and seroprevalence in U.S. children. We will review the

current RSV immunization recommendations for infants and young children, and then review data on the immune response after RSV immunization with nirsevimab. Throughout the first three sections of the talk, I will touch on several unmet medical needs and data gaps for pediatric RSV prevention, and we'll again summarize those at the end of the talk. Next slide. Next, please.

RSV burden is high in children less than five years of age in the United States. CDC estimates that each year among children in this age group, RSV leads to approximately 2 million medical encounters, 58 to 80,000 hospitalizations, and 100 to 300 deaths. Next slide. In the United States RSV is also the leading cause of hospitalization in infants. Overall, 2 to 3% of young infants in the U.S. will be hospitalized for RSV. All infants are at risk for hospitalization, including those who are born at term and those without underlying medical conditions. The highest RSV hospitalization rates occur in the first months of life and risk of hospitalization declines with increasing age in early childhood. Certain conditions further increase the risk of severe RSV disease in infants or young children as listed here. Next slide.

This slide summarizes laboratory-confirmed RSV-associated hospitalization rates across the lifespan for six seasons from 2018 through 2024. These rates are estimated from CDC's RSV Net Surveillance System, which conducts population-based surveillance in a catchment area that covers approximately 8% of the U.S. population. What we can see here in the darker red box on the left of the slide is that RSV-associated hospitalization rates are consistently highest among infants, particularly the youngest infants, compared to all other age groups. But now note in the lighter red box that there is a lower, but still substantial, burden of RSV-associated hospitalizations in children 12 to 23 months of age. After this age group, rates decline in older children and younger adults, before again increasing in older adult age groups. Next slide, please.

It's also notable that RSV-associated hospitalization rates in children less than five years of age exceed rates of other immunization preventable respiratory viruses, namely influenza and COVID-19. This slide shows hospitalization rates per 100,000 children—note the difference in scale from the prior slide,— where rates for RSV are shown in orange, COVID-19 in blue, and influenza in gray. Rates here are for last season, the 2023-2024 season, and are estimated from data from the New Vaccine Surveillance Network, which conducts prospective surveillance with systematic testing for the three respiratory viruses shown here at seven U.S. medical centers. What we see here is that in the youngest infant, 0 to 2 months of age, during last season, RSV hospitalization rates were approximately seven to tenfold higher than COVID-19 and influenza hospitalization rates. And RSV hospitalization rates remained elevated above those of COVID-19 and influenza hospitalization rates across all age groups through 59 months of age. Next slide.

We have seen thus far that RSV results in a high burden of hospitalization in children, but RSV is also a common cause of non-medically attended community level illness and infection in infants and young children, as has been documented by three U.S. longitudinal birth cohorts that are summarized here. The earliest of these cohorts was the pivotal Houston Family Study conducted from 1975 to 1980. The most recent of the cohorts was conducted from 2017 to 2020. So, all cohorts were conducted before the introduction of new RSV prevention products that we'll discuss later. All three cohorts conducted prospective surveillance with respiratory sample collection for RSV testing, as well as periodic serum collection, and that allowed the investigators to estimate cumulative incidents by age. Findings from these cohorts suggest that at least 50% of children have had at least one RSV infection by one year of age and at least 75% have had at least one RSV infection by two years of age. Next slide, please.

The Houston Family Study also observed that RSV reinfection was common in children less than five years of age. The investigators examined the relationship between preseason RSV neutralizing antibody titers, shown by the red box on the left of the table, and the frequency of reinfection, shown in the right box on the table-- Right red box on the table. And they observed that RSV reinfection risk was inversely associated with RSV neutralizing antibody titers, which suggests that neutralizing antibody played a key role in protection from infection. Next slide.

So, to summarize, RSV infection is common in infants and young children, with at least half of infants having an RSV infection by one year of age and at least three quarters by two years of age. RSV is also the most common cause of hospitalization in U.S. infants. The highest hospitalization rates are in infants, particularly the youngest infants, followed by children 12 to 23 months of age. And lastly, most hospitalizations in children less than two years of age occur in healthy infants and children. Next slide.

From here we'll transition to discussing current recommendations for RSV immunization in infants and young children. Next slide. There are currently two products recommended to protect infants and young children from RSV lower respiratory tract infection through passive immunization. All infants in their first RSV season are recommended for protection through either maternal RSV vaccine given to pregnant people at 32 to 36 weeks gestation, or through infant receipt of nirsevimab, a monoclonal antibody with an extended half-life. Some children in their second RSV season are also recommended for protection with nirsevimab and those are children in selected groups considered at increased risk for severe disease in their second season. The current recommendations for RSV prevention in young children highlight two gaps related to current prevention strategies. Next slide, please.

The first of these gaps is a data gap related to additional RSV vaccine doses in subsequent pregnancies after the first lifetime dose. Currently, the Advisory Committee on Immunization Practices recommends that people who receive a maternal RSV vaccine during a previous pregnancy are not recommended to receive additional doses during future pregnancies and infants born to people who were vaccinated only during a prior pregnancy should instead receive nirsevimab. These recommendations were made based on the absence of data on the safety, immunogenicity and effectiveness of additional RSV vaccine doses in subsequent pregnancies and in the U.S. contexts, where we have two recommended options for protecting infants from severe RSV disease. Next slide, please.

The second data gap is noted here in the terms of the groups recommended for second season RSV immunization. These groups include children with chronic lung disease, children with severe immunocompromised, and children with cystic fibrosis as well as American Indian and Alaska native children. Next slide, please.

Keeping the groups that we just saw in mind, this slide shows data from RSV Net on RSV associated hospitalizations and Intensive Care Unit admissions in children 12 to 23 months of age, an age group which approximates, but note is not exactly identical to the age group of children in their second RSV season. The data here are from the 2022-2023 season for illustration purposes. The Y axis shows us counts of children with each RSV-associated outcome, and in each bar the lighter blue shade shows the proportion of children with each outcome who are not in a high risk group currently recommended for nirsevimab receipt in their second RSV season. What we can see here is that overall, more than 90% of children 12 to 23 months of age hospitalized with RSV, as well as those requiring Intensive Care Unit admission, would

not have been eligible to receive nirsevimab in their second RSV season based on current recommendations. Next slide, please.

The Advisory Committee on Immunization Practices' decisions about which groups of children to recommend for nirsevimab receipt in their second RSV season were informed in part by cost effectiveness analyses. This slide shows key findings from those analyses which were recently published. The Y axis of this figure shows us the incremental cost effectiveness ratio, or ICER, where a lower ICER is preferable with respect to cost effectiveness. The X axis shows us varying costs of the recommended dose of nirsevimab for children in their second RSV season. The different colored lines show us different theoretical risk groups with 2, 3, 6 or 10 times the level of risk for an RSV-associated hospitalization compared to a base risk among the general population of children in their second season, which is depicted by purple. What this graph shows us is that the ICER of nirsevimab for children in their second RSV season is highly variable and strongly influenced by both product cost and risk level, where a lower product cost results in a lower ICER in children with lower risk. In other words, a lower cost per dose would make nirsevimab more cost effective in lower risk children in their second season. Next slide, please.

So from here we'll shift to an overview of data related to immune responses after RSV immunization with nirsevimab. Next slide. RSV fusion glycoprotein or F protein is a protein on the surface of the respiratory syncytial virus. The F protein facilitates virus entry into host cells and importantly it exists in two key states. The first is a prefusion confirmation, which is shown on the left in this figure. The prefusion F protein is the target of most neutralizing antibody after natural infection, and it is also the target of current vaccines and monoclonal antibodies. For example, nirsevimab

targets site Ø on the prefusion protein, which is depicted in red, and notice that that site is not accessible on the second confirmation on the right, which is the postfusion confirmation. So, antibodies to the postF protein can be used to differentiate responses to natural infection versus immunization in infants who have received nirsevimab. Next slide.

So, on the next two slides are summaries of serologic data from infants in two prelicensure, placebo-controlled, randomized trials of nirsevimab that provide insights about the immune response to RSV infection in children after nirsevimab receipt. The Phase II B trial with data shown on the left studied nirsevimab in preterm infants 29 through 34 weeks gestation. The melody Phase III trial on the right studied nirsevimab in term and late preterm infants. In this analysis shown here, the investigators examined geometric mean RSV neutralizing antibody titers, which are shown on the Y axis, over time starting at baseline before either nirsevimab or placebo receipt. Then again at either 31 or 91 days; at 151 days, which corresponded to the end of the RSV season; and then again once more at 361 days, which corresponds approximately to the start of the participant's second RSV season.

The lines on the graph show the trajectory of neutralizing antibody titers for four groups. The blue lines are the nirsevimab recipients, the gray lines are the placebo recipients. And the solid lines in each color indicate participants who had medically attended diagnostic-confirmed RSV infection, which was one of the outcomes in the trials, during the follow-up period. The dash lines in each color show participants without RSV infection. So, what we can see here is that participants started out with similar neutralizing antibody titers; that nirsevimab recipients overall then had higher neutralizing antibody titers than placebo recipients over time, irrespective of whether

participants had a medically-attended RSV infection during follow-up. Nirsevimab recipients also continue to have elevated neutralizing antibody titers at 361 days after receipt, suggesting some residual neutralizing antibody for those children going into their second RSV season. Next slide, please.

This slide shows data for the same analysis comparison groups, but here the investigators assessed RSV postF antibody levels over time to examine infant immune responses to medically-attended, diagnostically-confirmed RSV infection after either nirsevimab or placebo. Recall that nirsevimab binds specifically to the site Ø epitope on preF and doesn't bind postF. Thus, postF titers here can be attributed either to maternal acquired antibody, which wanes in the early months of life, or from natural infection. So what we see here is that antibody levels to postF increased in both nirsevimab and placebo recipients with medically-attended, diagnostically-confirmed RSV infection, with a slightly greater increase in titers in the placebo recipients, suggesting that infants with RSV infection still mount an immune response in the presence of nirsevimab, but responses may be slightly blunted compared to placebo recipients. The investigators also examined their proportion of participants who had sero-response to RSV exposure but who did not have a medically-attended, diagnostically-confirmed RSV infection in the study. They found that rates of sero-response to RSV postF were similar among nirsevimab and placebo recipients, suggesting similar rates of mild or subclinical infection despite differences in rates of more severe RSV illness in the trials. Next slide, please.

So, to summarize data from prelicensure nirsevimab trials suggest that nirsevimab results in higher neutralizing antibody titers than natural infection in infants, and titers remain elevated through at least one year. Data from the trials also suggest

that nirsevimab does not reduce rates of infant antibody response to natural infection, although antibody responses to natural infection after nirsevimab receipt may be lower compared to placebo. In the trial, 63 to 70% of all infants had evidence of sero-response to RSV exposure at the end of their first RSV season. Next slide, please. And next, please.

And I'll close here by summarizing several unmet medical needs and data gaps for RSV prevention products. And with respect to unmet medical needs, a clear need is low cost and effective RSV immunizations to expand protection to a broader population of U.S. children in their second RSV season. With respect to data gaps-- A data gap is needed data on safety, immunogenicity and effectiveness of additional doses of maternal RSV vaccine after the first lifetime dose during subsequent pregnancies. A second data gap remains the population level immune landscape in infants and young children in the era of new RSV prevention products, which may influence epidemiology of RSV in children as product uptake increases. Next slide, please.

And I'll close by acknowledging many collaborators who contributed to today's presentation. Thank you.

Epidemiology of Respiratory Syncytial Virus in U.S. Children – Q&A

Dr. El Sahly: Thank you so much, Dr. Dawood. I would like to invite my colleagues to use the raise-your-hand function should they have a question for Dr. Dawood, and I will kick us off by the first question and it pertains to unmet need number one that you highlighted in your last slide. We do know that the first season of nirsevimab was rolled out last year. The availability was very limited. The uptake was not where it'll eventually be as a status quo. So, potentially the dent that this particular preventive measure could make is not fully materialized yet. So, this year promises to be better.

And in light of the data you showed us, that the antibody-- Neutralizing antibody titers persist even up to year one, did any of the CDC colleagues perform modeling studies based on what you showed us looking at what dent into morbidity will nirsevimab have into year two or into season two for an average child or average infant?

Dr. Dawood: Thank you for that question. I'm not aware of any modeling studies looking at the impact of first season receipt of nirsevimab on second season illness. However, there was a publication from, again, the Phase II B and Phase III trial investigators from nirsevimab that looked at rates of medically-attended RSV illness in the second season and severity of illness. And what they found in their analysis was no difference in rates in the second season between nirsevimab and placebo recipients.

Dr. El Sahly: Thank you. Dr. Gans.

Dr. Gans: Thank you, Dr. Dawood, for that wonderful presentation which really got us started. I did have a question. You've spent some time elaborating what the immune or at least antibody responses after nirsevimab. Do you have comparator data after maternal immunization and how that actually affects the immunity of-- The immune response after those infants actually have attended RSV infection? So that we can compare them.

Dr. Dawood: I'm not aware of analogous data for maternal immunization-- Antibody from maternal immunization. Dr. Natalie Thornburg from CDC is joining me as a respondent and I'll just give her the opportunity to comment if she'd like to.

Dr. Thornburg: I'm also not aware of any data like that for parental immunization. Parental immunization would be a little bit more akin to infection of a pregnant person, excuse me, because a polyclonal response would be transmitted to the

infant, and we know that infants do mount antibody response after infection, because it happens all the time. So, we don't have that data, but it would probably be a little bit more similar to just a mother having high antibodies from previous infection.

Dr. Gans: Yeah, the question was really about the immune response of the infants, because we're doing a lot of analysis of what the nirsevimab or a passive immunity to just the fusion prefab. Anyway, I think those are important so we can understand which option for infants actually is most protective, especially in the global availability of some of these therapeutics. Thanks.

Dr. El Sahly: Dr. Sarah Long. Dr. Long, you're on mute.

Dr. Long: I'm sorry, my unmute button didn't work, but here we go. I have a follow-up question for Dr. Thornburg because I was surprised by her answer. I have thought that what the baby sees from either nirsevimab or prefusion vaccination of the mother is identical. Can you please educate us on why it would be different?

Dr. Thornburg: Wait, I'm sorry. Can you repeat that question Dr. Long? I want to make sure I understand exactly.

Dr. Long: Yeah. So, the mother who is immunized passes only antibody to the baby and she has received a prefusion vaccine that is not unlike nirsevimab, which is a prefusion antibody. But you said the maternal would more simulate the response of infection in the mother. Why would that be?

Dr. Thornburg: Because by the time a person is an adult, they have had many infections and there is data to suggest that through repeated infections in your lifetime, you get a very diverse antibody response that includes neutralizing antibodies against site Ø. It's not a single antibody. So nirsevimab is one single antibody that binds to

prefusion F, a very specific part of prefusion F. A person might have one antibody that looks like nirsevimab, but it's one in 10,000 antibodies. So that's just one antibody that gets boosted. A mother gets that vaccine, and they will be boosted presumably against prefusion F, but they should have many antibodies that bind prefusion F. So, all of those antibodies should be boosted against prefusion F, and so a maternal vaccination would not exactly mimic infection, but it would be a lot more like infection than just receiving a monoclonal antibody because it would be a very diverse antibody response.

Dr. Long: Thank you.

Dr. El Sahly: Thank you. And the last question comes from Dr. Kotloff.

Dr. Kotloff: Yes. I'm wondering about the concern related to nirsevimab interfering with active immunization responses and wondering if the level of maternal antibody shows a similar effect.

Dr. Thornburg: Likely, yes. If an infant has high levels of neutralizing antibody, whether through parental immunization or through a mother having high levels of neutralizing antibodies from previous infection that get transmitted to an infant, those high levels of antibody should abrogate replication in that infant. And so you should have some blunting of an antibody response because more virus replication makes more viral protein, and that more viral protein should drive higher titers of antibodies. So yes, that absolutely would be expected.

Dr. El Sahly: Okay. We're almost out of time, but Dr. Bernstein, last question.

Dr. Bernstein: Thank you. This is for Dr. Dawood. I just wanted to clarify, you had mentioned about 2 million medical encounters, 50 to 80,000 hospitalizations, 100 to 300 deaths annually. When someone looks at a cohort in a given year and compares those

children who have received nirsevimab versus those that have not received nirsevimab, are there differences there?

Dr. Dawood: Thank you for that question. I think it's too early for us to say in the United States for some of the reasons that Dr. El Sahly pointed out. Last season was our first season of introduction, there were some nirsevimab shortages earlier on in the season, and so I think we would hope that we would have more infants protected earlier in the season, in future seasons where we could look at impact like that at a population level. CDC does monitor that. For example, one of our systems, the New Vaccine Surveillance Network, is poised to look at hospitalization rates and be able to look at impact after introduction versus before, to get at some of the questions that you're asking.

Dr. Bernstein: Thank you for clarifying.

Dr. El Sahly: Thank you, Dr. Dawood and Dr. Thornburg. I would like to invite now Dr. Pedro Piedra. Dr. Pedro Piedra is a Professor, Department of MVM and Pediatrics at Baylor College of Medicine. Dr. Pedro Piedra will give us an overview of vaccine-associated enhanced respiratory syncytial virus disease, clinical and nonclinical aspects of RSV vaccine safety in young children. Dr. Piedra.

Vaccine-Associated Enhanced Respiratory Syncytial Virus Disease

Clinical and Nonclinical Aspects of RSV Vaccine Safety in Young Children

Dr. Piedra: Thank you, Hana, and good morning. May I have the next slide, please? This is a disclosure statement. Next slide, please. And this is more or less the objectives that I'm going to be covering. I will focus on the 1960's experience and what we have learned and not learned from that experience. Some of what we believe is the

immunology behind vaccine-enhanced disease, and then touch on what Fatimah had pointed out on promising vaccine development and the utilization of maternal vaccination and monoclonal antibodies in that context with promising vaccines as they're rolled out, and some of the safety parameters that we need to think about. Next slide.

But first I want to highlight that vaccines have done a tremendous good and the expanded program on immunization that started in 1974 has saved over 146 million lives of children younger than five years of age, and during this time, vaccination has accounted for 40% of the observed decline in global infant mortality. Next slide.

From a global perspective, we know that there are significant number of causes of mortality in children under five years of age. This was a study done in 2019 and I want you to point to the right table and note that lower respiratory tract illness is the major cause of death in children under five years of age. Next slide, please. And as Fatimah has indicated, RSV is a major global pathogen; causes significant lower respiratory tract disease. Something that we forget about, about a third of all pneumonia hospitalization in the U.S. included is caused by RSV. It is the leading cost of hospitalization for bronchiolitis. And annually, globally, there are in the range of 55,000 to 200,000 deaths that are attributed to RSV. And if one considers children under six months of age, almost every 15-- For 1 in every 15 deaths are caused by RSV in infants 28 days to less than six months. So, it has a significant impact globally. Next.

There is, without a doubt as a pediatrician, a major need for a safe and efficacious vaccine for children under five years of age. However, the experience of the 1960s that resulted in vaccine-enhanced disease upon natural RSV infection has delayed vaccine development for decades for this population. Next. So, I want to take you back

to the beginning. And this is Robert Chanock, that many of you all are aware, and was the one that put the link between RSV or, if you go to the next slide, between the chimpanzee coryza agent and RSV, and it became very quickly recognized in the early 1960s and late 1950s that RSV was a major pathogen for young children. Because of that—next slide— there was significant effort that was undertaken to develop a vaccine that could protect against RSV in infants and young children.

The vaccine was prepared, as it was standard practice at that time, with formalin inactivation and also alum precipitation. There were four trials that were done with the Pfizer formalin-inactivated RSV vaccine in 1966 and 1967, and they're listed here by these references in this table. I want to focus the attention to children 2 to 23 months of age because vaccine-enhanced disease was not observed in all children. And if one looks at the vaccinated versus the control group, and if we look at Kim in particular, those were the children that received the vaccine when they were the youngest. They also had the greatest impact with regards to vaccine-enhanced disease upon natural RSV infection. So, of those that were infected with RSV, 16 of 31, were hospitalized, of the formalin-inactivated RSV vaccine recipients versus 1 of 40 in the control group. Unfortunately, in that particular study, two infants died. Those two infants died at 14 and 16 months of age, upon natural infection with RSV. They were vaccinated. The first dose that they received was at two and five months of age. And in that study, most children received two or three doses, and the regimen was one month vaccination, then the following month, and then three months later. And these four trials, the vaccination- - The regimen for vaccination was somewhat different. But in general, they received two doses one month apart and the third dose may have been one month later or several months later.

The other study that I think is very important highlighted here by Dr. Kapikian is that of the children that were infected with RSV, 9 of 13 ended having pneumonia. And of the control group 4 of 47, or 9%, had pneumonia associated with their RSV. Next slide, please.

If we look a little bit more closely at the experience by the Kapikian study and look at those that had pneumonia in the context of formalin-inactivated RSV vaccination or in the control, one can see that they both had absolute levels of coryza. Cough was biased more in the vaccinees-- Formalin-inactivated vaccinees, so was wheezing. Rales was comparable between the two groups. And if one look at radiographic evidence of pneumonia, one could see that in the formalin-inactivated RSV vaccine, 10 of 11 had evidence of pneumonia, and 5 of the 13 were hospitalized compared to 1 of 9 in the non-vaccinated or 1 of 11, 9%, in the control group.

If we look at the study by Kim, I want to point out that the control arm received a formalin-inactivated parainfluenza vaccine, either parainfluenza vaccine type 1, and in other studies a triple combination of parainfluenza type 1, 2 and 3. The point that I want to state here is that in those infants that received the formalin-inactivated parainfluenza vaccine upon natural infection with parainfluenza or RSV, vaccine-enhanced disease was not observed. It was only observed in the formalin-inactivated RSV vaccine recipients that were naturally infected with RSV.

If we look at the study by Kim, we can see that at the end of three doses, the geometric mean neutralizing antibody titers and the vaccinees-- Formalin-inactivated RSV vaccinees was low at 48, versus the parainfluenza vaccinees, which one would expect is basically undetectable. If we look at RSV infection, they were comparable between the two groups, so there was not an enhanced RSV infection rate in those that

received the RSV vaccine. If we look at the number of hospitalizations, 80%, or 16 of the 20 that were infected with RSV ended up in the hospital compared to 1 of 21 for the parainfluenza vaccinee. The mean length of hospitalization was much longer. Likewise, the diagnosis of pneumonia was 95% in the RSV vaccinees versus 19% in the parainfluenza vaccinees. And very unfortunately, there were two deaths. Next slide.

If we look at the study by Fulginiti, this was a study-- A larger study that was conducted. Here the control group was the triple parainfluenza vaccine that was formalin-inactivated and they vaccinated children beyond two years of life, and one can see very clearly, if you look at the age group of 6 to 11, the risk-- And go to the very far right column. The risk for hospitalization was 13.7 per 100 children versus 1.5 in the control group. As the age increased 12 to 23 months, there was still a significant increase at 5 per 100 versus 0.92, and over 24 months of age there is no longer an increased risk for hospitalization attributed to the formalin-inactivated RSV vaccine followed by RSV infection. Next.

What people often forget is the Merck experience also with a formalin-inactivated RSV vaccine, also conducted during the 1966-1967 seasons. And their vaccine was very similar to the Pfizer vaccine. It was formalin-inactivated, it was concentrated, it was alum-absorbed. A major difference was they often combined it with other vaccines or other antigens, whether it be parainfluenza or mycoplasma or even more flu. And also the age group was older. However, I do want to call to your attention that there were age groups like Woodhour, where children were one year of age and younger, where the vaccine induced very poor neutralizing antibody response and there is no evidence of enhanced disease. In fact, in somewhat older children, three to five, there may have been evidence of some degree of protection, very low, against severe

RSV disease and about 40% of the children were at that time considered seronegative based on the assay used. Next slide.

To date, a clear mechanistic understanding of the formalin-inactivated vaccine-enhanced disease has not been established, although there are leading immunological mechanisms that are considered plausible. But first, just a little bit about the virus to better understand the immune response and vaccine development. Next.

As Fatimah has already indicated, RSV is a negative-sense, single-stranded RNA virus. The two major surface glycoproteins that induced a host neutralizing antibodies are the G, which is heavily glycosylated and important in viral attachment, and the F, which is well conserved among the two subgroups RSV A and RSV B and required for fusion to the cell. In recent years. In the last decade, one of the major contributions made in the RSV field was the understanding that the F protein came in more than one form. And the form that we had not realized was the prefusion form that is required for infection. That is the active form of the fusion protein and it has some unique antigenic sites, such as site Ø, which nirsevimab targets; site V; and then in the postfusion form, which is the stable form, but it's no longer an active form, there are some shared sites that one can find in the prefusion and postfusion, and that's site IV and site II. Site II, as you may recall, is the target for palivizumab, which was used very effectively to prevent severe disease in a very select subgroup of high-risk infants. Next.

What does the formalin inactivation do as well as heat treatment over a three-day period, which is the way the Pfizer and Merck vaccines were produced. They were formalin-inactivated and they were heat treated over a three-day period, concentrated and absorbed, and using monoclonal antibodies that target both unique sites and shared sites. One can see what happens under these treatments. Motavizumab, which targets

site II, which is shared by both the prefusion and postfusion form, remains equally bound to the target over time. But that is not true for the monoclonal antibodies that target unique sites on the prefusion form. AM14 that targets site V and D25 that targets site Ø. And with the disappearance of the binding over a 24 to 48-hour period, one can see in the illustration figure on the far right that the virus loses its ability to infect the whole cell during that time period. So, basically formalin inactivation transitions the preF to a postF form. Next.

So, in my opinion, the antibody response as an unlikely cause of the formalin-inactivated RSV vaccine-enhanced disease. And I'll show you some data why I think so. Next. First, this was an important study that was done by Murphy and others using serum that had been stored from the original Kim study and this is the one where there was the highest hospitalization rate. And if one compares the formalin-inactivated RSV vaccine group, this is two to seven months, versus the formalin-inactivated parainfluenza vaccine control, again two to seven months, versus natural infection. And this is complicated, so I'm not going to go over all the binding and neutralization, but what I'm going to show you is if you go to the far right column and look at the ratio of binding antibodies to neutralization or neutralizing antibody titers, and this is in log 10, you can see that for those that received the formalin-inactivated RSV vaccine, they had a high binding to neutralizing antibody ratio; 251 to 1, versus natural infection, which was 12.6 to 1. Or the formalin-inactivated parainfluenza vaccine, which means that's maternal antibodies that the infant has at that time, which again shows a ratio of 10 to 1. So, basically the vaccine-- Formalin-inactivated vaccine is inducing poor neutralizing antibodies but high binding antibodies. Next.

So, what do we know about some animal data? First, in humans, the formalin-inactivated appears to have induced high titers of binding antibodies with weak to moderate neutralizing and fusion-inhibitory activity consistent with low avidity antibody response. These antibodies in the context of a large antigen load is thought to have led to immune complex deposition and complement activation in the airways of infants upon subsequent RSV infection. Vaccine-enhanced pathology can be mediated by immune complexes and abolished in complement component C3 and B cell-deficient mice. The two infants who died from vaccine-enhanced disease had peribronchiolar deposition of C4d, a complement cleavage marker of complement activation by the classical pathway. However, cell-bound C3 is present during the convalescent phase of natural RSV infection and RSV antigen-containing immune complexes are easily detectable in the upper airways of infected infants from three days up to 36 days after illness onset. Also, antibodies induced by the formalin-inactivated RSV vaccine, either passively administered or maternally transferred, have not been associated with vaccine-enhanced pathology in the cotton rats or mouse model for vaccine-enhanced pathology studies. Next.

This is the first study that was ever done in pregnant women with an RSV vaccine and it was a purified fusion protein vaccine that we think was mostly in the postF form. And if one looks at the far right column, that vaccine induces very low levels of neutralizing antibodies that were passed to the infant. I'm not showing you here the binding antibodies through the fusion protein, but they were elicited strongly, and the infants were followed for one to two years following birth and none of them had any safety concerns or vaccine-enhanced disease experience following RSV season. Next.

So what about the cellular immune response as a potential cause of the vaccine-enhanced disease? Next. So there was a study done by Kim et al. with the population that received the original formalin-inactivated RSV vaccine, and they looked at the lymphoproliferative response after they had learned about the vaccine-enhanced disease. 12 of the 21 formalin-inactivated RSV vaccinees were infected with RSV before the lymphocyte collection was performed. And so I'm going to call your attention to the percent transformation for the formalin-inactivated RSV vaccinees; whether they were infected with RSV or not, it was increased compared to the formalin-inactivated parainfluenza vaccinees, their control group. Very importantly, the cell in which the virus was grown to produce the formalin-inactivated RSV vaccine was not associated with increased lympho proliferation as observed here. And if one looked at the serum antibody response that was detected, the plaque reduction neutralizing antibodies appear to be of good titers. But if you look at those that were not naturally infected, it suggests that it may have been mostly derived from the mother-- Maternally derived. And they had generated complement fixing antibodies. Next.

So, if we look at the animal models and what have they provided, what insight have they provided, it suggests that the formalin-inactivated RSV vaccine has induced a Th2-biased CD4 T cell response, and after a natural RSV infection results in an eosinophilic parabronchial infiltrate and neutrophilic alveolitis, resulting in the vaccine-enhanced disease phenotype. The biopsy mouse model, the cotton rat, and the African green monkey have often been used to study this, and these models are semi-permissive to RSV. You require high virus load to infect them. In the mouse model, formalin-inactivated RSV priming in RSV-naïve mice has been linked to an imbalance Th2 response with production of IL-4 and IL-5 with pulmonary eosinophilic response upon experimental RSV infection and enhanced mucus production, airway

hyperresponsiveness and a reduction of cellular cytotoxicity activity. This Th2-biased immune response appears to mediate airway hyperreactivity and mucus hypersecretion. And in addition, a CD4 cell producing TNF-α appears to be associated with airway obstruction in the mouse model. The recombinant RSV G protein vaccine has also been associated with vaccine-enhanced pathology with increased cellular infiltrates in the lungs and a Th2-cell mediated IL-13 induced mucin hypersecretion.

Although the CD4 imbalance seems to be a major culprit for vaccine-enhanced disease, I want to indicate that memory CD8 T cells with high interferon production in the absence of RSV-specific CD4 T cells and antibodies will result in viral clearance but also lethal immunopathology. So, in the animal model, enhanced pathology results from-- Appears to result from an unbalanced T cell priming rather than infection enhancing or sensitizing antibodies. Next.

So what are vaccines that are not associated with vaccine-enhanced disease? Next. An early study was conducted with a live RSV vaccine that was administered subcutaneously. The live RSV vaccine was about 10^4 tissue culture infectious dose, and was produced in WI-38 cells. And there was no evidence of vaccine-enhanced disease upon RSV infection. If you look at the far down, neither protection against RSV disease or development of vaccine-enhanced disease was observed with RSV infection in these vaccinee groups, in particular in children under 24 months of age. Next. If one looks at vaccine-enhanced disease has not been observed with live RSV vaccines administered intranasally. This was a nice overview by Peter Wright and others that demonstrated about eight years of experience with seven different live RSV vaccines administered intranasally to infants and young children and whether they received two doses when they were 1 to 3 months or one dose when they were 6 to 24 months of age, there is no evidence of enhanced disease when they get infected with RSV. Look at the middle

column compared to the control, or the far right column when you look at more severe disease; it was very comparable between both groups. Next.

Fatimah has already commented that there are two new preventive measures and this has been a major breakthrough. It has been six decades in waiting that maternal antibodies with a preF vaccine against both RSV A and RSV B has been approved, as well as the long-acting monoclonal antibody called nirsevimab that targets site Ø and there have also been three vaccines that have been approved for adults 60 years of age and older. Next. In the pipeline, there are five vaccines that are being targeted for pediatrics. The vaccine in Phase III, a live/chimeric RSV vaccine by Sanofi. Vaccine in Phase II, a parainfluenza 5 vector vaccine. And in Phase I the codagenix. There's a protein-based vaccine based on the G-- The central conserved domain of the G protein, and then there's the Moderna vaccine. Next.

So we need to study RSV vaccine immunogenicity that targets young children in the context of other preventive measures that protect infants against severe RSV infection, and that has been stated very nicely by Dr. Dawood. Next. This is just to remind you that there was very good evidence of protection against lower respiratory tract disease in infants born to mothers that received a prefusion F vaccine that lasted for at least six months. Next. And likewise with nirsevimab that was given to late-preterm and term infants, there is a significant reduction in hospitalization and medically attended RSV lower respiratory tract disease. Next.

So, one needs to think about the risk versus benefit ratio of RSV vaccines for young children. We know that there is significant benefit if we can protect against severe disease and so one needs to kind of de-risk the risk that may be associated with vaccines in the very young. And so it's important to define the immune profile and

safety in preclinical animal models. It is important that the vaccine formulation be determined or nearly settled before going into the pediatric population. Depending on the vaccine, it is important that it be stable and non-transmissible. We need to be able to accept-- Establish an acceptable reactogenicity profile initially in adults as one progresses into children and ensure there's no significant safety signals that are observed for participants followed during one to two RSV seasons, initially in RSV-experienced children and later in RSV-inexperienced infants. And now that we have new methods for protection, we need to study them in the context of RSV maternal vaccination and nirsevimab and potentially other immunoprophylaxis compounds that will come later. Next.

And so, what are some of the major safety concerns for RSV vaccine in young children? I think we all know vaccine-enhanced disease is a significant major concern for children under two years of age, but you also need to think about adverse events of special interest and that will be likely driven by the platform in which the vaccine is presented. Just as some examples, issues with febrile seizures possibly with adjuvanted or high dose vaccines or during co-administration, autoimmunity with new adjuvants, wheezing illness or respiratory distress with live-attenuated vaccines or intranasally administered vaccines, systemic illnesses with vector-based or messenger RNA vaccines.

And to finish-- Next. So, what are some of the characteristics that one would like for an RSV vaccine for children: to have a safety profile demonstrated that causes no or mild transient reactogenicity with no evidence of vaccine-enhanced disease; to have high level of efficacy against confirmed severe RSV disease caused by both RSV A and RSV B subgroups; determine the impact on non-severe RSV disease and also on recurrent wheezing and other respiratory viruses; establish an immune profile of the

vaccine and hopefully correlates a protection; co-administration with other vaccines and demonstrate their safety and non-inferior immunogenicity; and lastly with these new preventive measures, understand whether there's an interference that may be occurring with maternally acquired or monoclonal antibodies on vaccine immunogenicity. With that, thank you.

Clinical and Nonclinical Aspects of RSV Vaccine Safety in Young Children – Q&A

Dr. El Sahly: Thank you so much, Tony, for going over a very complicated and involved topic in such a short time. We learned a lot. I would like to invite the Committee members to use the raise-your-hand function to ask a question to Dr. Piedra and I will begin by one brief question. To your knowledge, was the Merck product, the formalin-inactivated that was given to seronegative infants but didn't result in vaccine-enhanced disease, compared to the other formalin-inactivated products in an animal model where a particular-- The immunology was dissected to these two in a head-to-head animal model study?

Dr. Piedra: The answer is no. One, with the Merck study, I'll just point out that most of the studies were done with somewhat older children, although there were some with one year of age and older. But something that was unique with the Merck study that was not done with a Pfizer study is that in general these were polyvalent vaccines, so they contained more than just RSV and that may have had an impact on altering the type of response that one saw during vaccination.

Dr. El Sahly: Yeah, so that particular alteration with modern immunology would've been interesting to dissect, especially with the low predictive value of many of these animal models. Dr. Gans?

Dr. Gans: Thank you, Dr. Piedra, for that. I did have a question because it seems like we're sort of dancing around the idea that we need a comparator of what an immune response to actually natural infection is in terms of how that compares to a vaccine response and what in particular is causing-- Because it appears that someone who's immune who then gets vaccinated doesn't get enhanced disease, rather someone who's naïve, who gets the vaccines that we're giving them, has the potential for then on subsequent exposure being at risk for enhanced disease. I know that the model that we're all worried about are these formalin inactivated. I mean, the same thing happened with measles, which happens to be in the same paramyxovirus family. We understood that it was also-- I mean, the immunology is not settled but there does seem to be non-neutralizing antibodies in both those scenarios. I know that your evidence is also showing some impact of the cell-mediated immunity. Clearly, though, natural disease will give us likely not a shift to the Th2, but a good CD4 Th1 response. So I'm wondering-- My question really is around is there the-- I think what we need actually is very settled and better data on what actually an RSV infection does to the immune system that is helpful in predicting how these immunizations given as a primary response could be protective, and I'm not sort of hearing that or seeing that information coming forward, because-- And then I'm not seeing the difference between the immune response in children who are already immune getting vaccines versus those who are not, so that we can start parsing out what are the things that we should be looking for.

Dr. Piedra: That's an excellent question. We do know that under the umbrella of maternal antibodies that when an infant becomes infected with RSV, you don't see much of a neutralizing antibody augmentation, and whether the maternal antibody is attenuating the response or whether you're not able to see the response it's happening, but because they have maternal antibodies on board, you're not seeing an enhancement

of it. As they get older, still under a year of age and out of the influence of maternal antibodies, we have done some studies to demonstrate that the major site that we appear to be detecting is actually to site IV and site II, and that would make sense because these infants with primary infection don't mount a very robust neutralizing antibody response as you would see with reinfection, where later on site I or your prefusion sites become more dominant. And so it may be that maternal antibodies or low levels of maternal antibodies may interfere with some of the sites that are directed to-- That are unique to the preF, and that is why we may be seeing a site II, site IV response. Depending on the studies that we look at with cellular immunity, there is really a broad-- What I would say, broad level of-- Let me restate this. Timing of infection matters and when you're very young it suggests that you may actually have more of a Th2 type response in the very young, and as you get older you develop more of a balanced response. And so in my mind, I think an important aspect as we begin vaccinating children having a balanced response both from an antibody perspective and a cell-mediated immune perspective is highly relevant.

Dr. Gans: Thank you very much.

Dr. El Sahly: Dr. Perlman.

Dr. Perlman: Yeah, so I have a question I think that follows up on that question. So, one of the things that was striking in the information that you presented was the fact that CDA T cells by themselves could cause severe disease. So, here we're not dealing with Th2 responses or antibodies, but we have what might be considered-- What might've been expected to be a protective response. Do you think it led to lethal disease because, as a word, "too much of a good thing" or that the absence of antibodies made this effect so overwhelming? So, this might suggest that the mechanism could be more than one

way of getting to a lethal disease here, because it could either be too much of the right response or a response that's dysregulated. I just wanted to know your thoughts.

Dr. Piedra: Agree totally. That was work done by Steve Varga and others, and they highlighted very nicely that it cleared the virus. So, viral infection was cleared, but it caused significant airway disease and so there was a lot of cell damage that was occurring, and these mice that normally don't succumb to RSV infection, did. And so it was like you stated; too much of a good thing. And so that's why I keep on saying that we don't know exactly the right immune profile that one needs, but it appears to be a balanced profile that is needed and nothing too much in excess.

Dr. Perlman: Thank you.

Dr. El Sahly: Dr. Long?

Dr. Long: Yes, thank you so much. This just keeps getting more and more complicated. I have two-- First an observation of pertussis vaccine. It's the primary, your first experience with the vaccine, that biases if it's a cellular, a Th2 response, that gets worse and worse and worse and worse the more you see pertussis vaccine. So, I don't know how or if RSV vaccines would become more balanced with time, but-- Maybe your thoughts about that. But my other question really is we talked-- You showed experienced and inexperienced infants, and the question is where do you consider the infant who has had passive protection from maternal antibody, that I've just learned today is a little different from nirsevimab, because they're both experienced in a way and it's when that neutralizing antibody begins to fade in the sixties, in the formalin-inactivated, that the badness became. So do we have to have a truly naïve-- Do we have to consider-- When we're thinking about safety, do we have to consider a truly naïve, somebody who didn't get a preventive passive protection, as well as those who

are naïve but had prophylaxis and the rest of everybody who might've already had infection? It's going to be increasingly difficult, I hope, to find babies who have not received passive protection one way or another because it's so effective.

Dr. Piedra: I think the scheme that most-- And I won't speak for industry, but one can see the studies, that the target population is generally going to be six months of age and older. And before, we had preventive measures; maternal antibodies by six months most would have been cleared. So that when one then becomes vaccinated or enrolled in those types of studies, they are both seronegative and RSV inexperienced. So, normally when we think about RSV experienced, we're thinking about infection rather than antibodies, and one can with serologic assays distinguish most of the time whether you've been infected or whether it was maternally derived or in this case nirsevimab-acquired. And so the issue for the vaccine-enhanced disease was mostly RSV inexperienced. They received the vaccine; many infants received the vaccine under the influence of maternal antibodies and it was the youngest when they were vaccinated that had the worst outcome later when they were exposed to RSV compared to older infants or young children when they were vaccinated and then subsequently infected. So, there was something unique with the vaccination regimen that whether it was in the presence or in the absence of maternal antibodies, making those infants susceptible to enhanced pathology and enhanced disease.

Dr. Long: Thank you.

Dr. El Sahly: My question now is to Jay and Karen. Can your question wait for the discussion portion of the meeting which is a two-hour time slot? Because we are a bit behind on time. Is that okay? Okay, thank you. Thank you, Tony, and I'm sure many of us will have a whole lot more to ask you in the discussion portion. I would like to invite

now our Moderna colleagues, Dr. Christine Shaw, Vice President, Portfolio Head, Infectious Disease Vaccines, and Dr. Matthew Snape, Vice President, Clinical Development, Infectious Diseases, Paediatric and Maternal Vaccines at Moderna. They will give us a review of investigational RSV mRNA-1345 and RSV human metapneumo mRNA-1365 vaccines and infants and children under two years of age. Take it away.

Moderna Presentation: Review of Investigational RSV (mRNA-1345) and RSV/hMPV (mRNA-1365) Vaccines in Infants and Children < 2 Years

Dr. Shaw: Good morning. We would like to thank the FDA for the invitation to review Moderna's pediatric RSV vaccine programs today. My name is Christine Shaw and I'm the Portfolio Head of Infectious Disease Vaccines at Moderna. As background for today's presentation, the Moderna RSV vaccine, mRESVIA, is licensed for use in adults above 60 years of age as of May, 2024. Safety and efficacy were demonstrated in a large global Phase III study. The only RSV hospitalizations in the study were in placebo recipients. We've also been developing this vaccine for pediatrics given the significant unmet medical need, and we've taken a conservative stepwise approach. Development has been in consultation with multiple regulatory agencies and following established RSV vaccine guidance. In a recent Phase I trial, we have identified a potential imbalance of severe or hospitalized RSV in RSV-naïve infants, five to seven months of age, with more cases in the vaccine than the placebo recipients. Specifically, 5 out of 35 children, or 14%, in the vaccine group; in 1 out of 18, or 6%, in the placebo group. We have paused study dosing in July. There has been no subsequent enrollment or dosing since, and surveillance continues. There's currently no plan to continue this program in children under two years of age.

Our goal today is to share our available data to help inform pediatric RSV vaccine guidance and development. Here's our agenda. I will provide a brief introduction and share our nonclinical data, and my colleague Matthew Snape will then describe the clinical program.

As you heard this morning already, respiratory syncytial virus is the leading cause of infant hospitalizations in the U.S., with about 17 of every thousand children under six months of age hospitalized for RSV each year, and nearly every child has had at least one infection by two years of age and lifelong sequelae such as wheezing and asthma are common. The recent licensure of a maternal vaccine and a monoclonal antibody for infants have begun to address the pediatric burden. However, there remains a high unmet need for prevention of RSV in young children through active immunization. So, human metapneumovirus is closely related to RSV, and is similar in terms of virology, epidemiology, seasonality and disease. hMPV is the third most common cause of community-acquired pneumonia in young children, and more than two of every thousand children below 11 months of age are hospitalized from RSV-- From hMPV, sorry. Most children have been infected by five, and there is no specific vaccine or treatment available.

Before introducing Moderna's pediatric vaccines for these two viruses, I'd like to take a moment to touch on the history of pediatric vaccine development. A formalin-inactivated, called RSV vaccine, formulated with alum was studied as an intramuscular injection in the 1960s. As you've heard this morning, this vaccine resulted in enhanced respiratory disease, or ERD, in RSV-naïve infants after subsequent natural RSV infection. In a study that enrolled infants aged two to seven months, 80% of subsequently infected children were hospitalized and two died. After decades of research, it is thought that the contributing humoral factors to ERD included induction

of very little neutralizing antibody, which led to lack of virus control, and also induction of non-neutralizing binding antibody which led to immune complex deposition and associated complement activation in airways.

A likely contributing cellular factor was a high T-helper type two response resulting in airway inflammation. There is also increased understanding about what does not cause enhanced respiratory disease. RSV-experienced children and adults are not considered at risk. Specifically, ERD has not been observed after repeat natural infection or after vaccination of RSV-experienced children or adults. As for RSV-naïve infants, the perceived risk of ERD is dependent on the vaccine type. Some vaccine types were considered lower risk for ERD because they induce an immune response profile that is similar to that induced by natural RSV infection. This includes live-attenuated viruses and messenger RNA. These vaccine types incorporate intracellular antigen processing and host cell expression. mRNA is manufactured differently than formalin-inactivated RSV and has a different mechanism of action.

So, to address the need for pediatric RSV and hMPV vaccines, Moderna is developing two mRNA-based lipid nanoparticle-encapsulated vaccines. The first is RSV vaccine mRNA-1345, or mRESVIA, which as I mentioned earlier is already licensed for use in older adults. This vaccine encodes the membrane-anchored fusion protein stabilized in the preF confirmation. The second is a combination vaccine against RSV and mHPV, and it's called mRNA-1365. It also contains a second mRNA that encodes the membrane-anchored fusion protein of hMPV. These two mRNAs in the vaccine are present in an equal mass ratio. Both of the vaccines are delivered intramuscularly. The same mRNA platform is authorized or licensed to prevent COVID-19 in persons above six months of age. No enhanced respiratory disease has been reported with the licensed RSV vaccine or COVID-19 mRNA vaccines.

So a bit more about the RSV preF antigen encoded by these vaccines. RSV F protein is highly conserved across the A and B subtypes. It exists in two confirmational states: prefusion and postfusion, as shown on the right. The preF antigen was selected for the vaccine because the protein surface displays all of the antigenic sites known to elicit potently neutralizing antibody. This includes sites unique to preF as well as sites that are shared between the preF and postF confirmations. Therefore, our RSV vaccine was rationally designed to focus the immune response on the parts of the protein that induce protective immunity. Formalin-inactivated RSV, on the other hand, does not display any of the sites unique to preF. Those sites were destroyed by the formalin and heat inactivation process used to produce that vaccine.

Given the history of ERD, Moderna has taken a conservative approach to pediatric RSV vaccine development. It is aligned with established RSV vaccine guidance. So, the guidance states nonclinical studies should discriminate a candidate vaccine from formalin-inactivated RSV, and clinical evaluation should proceed stepwise from adults to RSV-experienced children and before RSV-naïve infants. There is no specific hMPV vaccine guidance that we are aware of, and no clinical precedent of hMPV ERD. However, given the similarity of these two viruses, Moderna has applied the same conservative approach to pediatric hMPV vaccine development.

So, now I will share our nonclinical data. These data have recently been submitted for publication and you can find the pre-print on the link shown on the slide. So, the WHO guidance outlines nonclinical testing requirements for pediatric RSV candidates in more detail: In at least one animal model, the candidate vaccine should induce neutralizing antibody; it should avoid deduction of excess non-neutralizing antibody; it should avoid a Th2-biased response, and it states a CD8 T-cell response may be helpful; and it should avoid lung inflammation and specifically alveolitis after

challenge from RSV. Overall, this profile will differentiate the candidate vaccine from formalin-inactivated RSV.

So, we have followed this nonclinical guidance in the evaluation of our RSV mRNA vaccines. Shown here in mice, both vaccines induce a strong RSV neutralizing—on the left plot,—and binding antibody—in the middle plot—against the preF confirmation. The formalin-inactivated RSV vaccine shown in orange on these images also induces RSV antibody, but as mentioned earlier, they are not neutralizing and they bind only to the postF confirmation as shown in the right panel. In terms of a cellular response, both RSV and mRNA vaccines induce a T helper type 1 CD4 T-cell response. That means they produce more interferon gamma than IL-5 and this is shown on the left plot. The mRNA vaccines also induce a strong CD8 T-cell response as shown on the right. In contrast, formalin-inactivated RSV induces an IL5-based T helper type 2 response on the left, and it does not induce a CD8 response.

We have also evaluated the RSV vaccine in the cotton rat RSV challenge model. We closely followed the WHO guidelines when designing this study, and this includes a number of important study controls. We tested a wide dose range of the RSV vaccine as administered as a two-injection series. A single injection of 0.3 microgram was also included, because it induces a weak immune response that provides just partial protection. This is an important condition under which to evaluate enhanced respiratory disease, given the formalin-inactivated virus induces a weak immune response and provides partial protection. The ERD positive control was formalin-inactivated RSV, and the ERD negative control was RSV infection. We also included a number of other negative controls to demonstrate the specificity of the response.

So, in cotton rats shown here, the RSV mRNA vaccine shown in blue induces a dose-dependent RSV neutralizing and preF binding antibody response shown in the left and the middle panels. The magnitude of the antibody response is similar or higher than the response to RSV infection which is shown in green. In contrast, formalin-inactivated RSV shown in orange induces antibodies that only bind postF and have weak or no neutralizing activity, similar to what we saw in mice. The immune response induced by the mRNA vaccine provided dose-dependent protection from an RSV challenge in the cotton rat model, as demonstrated by undetectable virus in the lungs of animals that received a high mRNA dose—in the left panel—compared to the negative control groups shown in gray. And as mentioned, a single 0.3 microgram mRNA dose, now highlighted in yellow, and this dose induced a weak immune response. It provided only partial protection, as you can see on this left plot. The protection mediated by the vaccine was not associated with lung type 2 cytokines, as represented in the right panel by IL-5-- IL-4. As expected, formalin-inactivated RSV—shown in orange—provided partial protection from RSV challenge and did have an IL-4 response in the lung.

So after the RSV challenge, cotton rat lung inflammation was evaluated by histopathology. The formalin-inactivated RSV induced the characteristic enhanced lung alveolitis and overall inflammation shown on the two panels. The RSV mRNA vaccine in the blue did not promote alveolitis or overall lung inflammation. Instead, the lungs from these animals appeared similar to those in the negative controls in green and gray. These data together demonstrate the RSV mRNA vaccine does not induce enhanced respiratory disease in the cotton rat model, even with a suboptimal 0.3 microgram single dose vaccination highlighted in yellow.

So, to summarize our nonclinical findings. We conducted studies in mice and in cotton rats, and we demonstrated the mRNA RSV vaccines induce protective immune

responses without enhanced respiratory disease. The profile induced by the mRNA vaccine is clearly distinct from that induced by the formalin-inactivated RSV vaccine. These data not only fulfilled the nonclinical testing requirements for pediatric RSV vaccines, but were very reassuring to us and to regulators, and they supported evaluation of the vaccine RSV-naïve children. We also conducted a similar set of nonclinical studies to de-risk hMPV enhanced respiratory disease with our combination RSV hMPV vaccine. So, formalin-inactivated hMPV also causes enhanced lung inflammation in the cotton rat model after hMPV challenge, as shown in the first column on this slide. As expected, the profile induced by our hMPV mRNA vaccine looks very similar to that observed with the RSV mRNA vaccine, and both look different from the formalin-inactivated viruses. So altogether the nonclinical data were very reassuring and they supported the clinical evaluation of both the RSV and RSV hMPV combination vaccine into RSV and hMPV-naïve infants.

So now I will pass the presentation to Matthew Snape who will share a summary of our pediatric clinical data.

Dr. Snape: Many thanks, Dr. Shaw, for providing that background and for presenting the nonclinical data. My name is Matthew Snape and I'm a pediatrician who is the Clinical Lead for Pediatric RSV Vaccines at Moderna, and I'll present on our current status of our RSV Pediatric Vaccine Program. Prior to initiation of clinical trials in under 2-year-old children, we demonstrated the immunogenicity and safety profile of both the RSV and hMPV components in adults and in seropositive 1 to 4-year-old children. The hMPV component was initially evaluated in combination with parainfluenza virus 3, PIV3, another important respiratory virus. While the hMPV/PIV3 Program has not continued, the hMPV component was then brought into a new combination with RSV, hence the RSV hMPV vaccine. These therefore provided the

appropriate data to allow progression of both the RSV and combination RSV hMPV vaccines to under 2-year-old children, according to international guidelines.

I will now present the results from our under 2-year-old RSV and hMPV study. These are also available online at the pre-print shown. The study design for 5 to 23-month-old children was developed in consultation with regulatory agencies and involved children 8 to 23 months receiving either the standalone RSV vaccine, the combination RSV hMPV vaccine, or placebo. These were administered as three intramuscular injections given two months apart. Following the DSMB review of data from these children, we could then age de-escalate to enroll 5 to 7-month-olds, with the initial cohorts receiving 15 micrograms of RSV or RSV hMPV, followed, after further DSMB review, by a dose escalation to 30 micrograms. Also, we have enrolled 8 to 11-month-old children to assess the impact of prior receipt for the monoclonal antibody nirsevimab on RSV vaccine safety and immunogenicity.

Here are the study objectives. Of note is that the primary objective was the safety of vaccines, with the secondary safety objective of evaluation the occurrence of RSV and hMPV infections over two complete RSV seasons, thus allowing compliance with international RSV vaccine evaluation guidelines. And of course we evaluated the immunogenicity of these vaccines.

The surveillance for RSV and hMPV illnesses was undertaken in an active manner during the local RSV and hMPV seasons. Parents received weekly prompts to complete an e-diary reporting new onset respiratory symptoms, following which an in-person visit was arranged within five days of symptom onset. Should two or more severe RSV or hMPV LRTIs occur, then a pause rule would be triggered. This allowed

for a very active process of monitoring, reporting, and acting on any concerns regarding excess severe RSV hMPV LRTI cases.

As will be discussed, this dosing pause was triggered in July. Here are the protocol definitions for the severity of respiratory infections which were derived from WHO guidelines. When implementing these, it was identified that a post-hoc composite definition of severe LRTI, very severe LRTI, or hospital admission as highlighted by the orange box, was best able to distinguish the most clinically significant LRTIs. And it is cases meeting this composite definition of severe hospitalized RSV illness that we'll focus on when discussing severe disease.

This study greatly benefited from oversight by an independent Data and Safety Monitoring Board with the responsibilities as shown, as well as overseeing age de-escalation and dose escalation, that the DSMB has been extensively involved in monitoring the respiratory surveillance and the decision to initiate and maintain the pause of further dosing in this study.

Lastly, before moving on to results, here are the definitions of RSV-naïve or experienced we will be using, which are based on postF binding IgG antibody concentrations at baseline. PostF antibody concentrations were used given that they're minimally impacted by prior receipt of nirsevimab, so they could be used for all cohorts in this study. The threshold used for different age groups are shown here with the younger children requiring a higher threshold due to the presence of maternal antibody.

I'll now present data from the age 23-month-old part of the study starting with immunogenicity and then safety data. This section of the study enrolled 90 children aged 8 to 23 months nearly all of whom received all three doses of vaccine or placebo. As can be seen, 42% were RSV-naïve at baseline. Sixty-five of these children were

recruited in Panama and 25 in the USA. Shown here is evidence of a robust increase in RSVA neutralizing antibody titers in 8 to 23-month-old children as measured at one month after each of the three study injections given at two-month intervals. Here the lighter colored lines represent participants classified as previously RSV-experienced, and this population responded well to a single dose of vaccine. By contrast, RSV-naïve participants, represented by the darker lines here, required two or three doses before achieving similar neutralizing antibody titers.

We also saw a robust binding IgG response. And when looking at the ratio of preF to postF antibody concentrations, we see a marked preF bias. This is especially pronounced amongst those who are RSV-naïve at baseline shown in the top row here.

T-cell responses showed a marked Th1 bias in keeping with the preferred cell immune response outlined in WHO guidelines. These responses were evaluated at one month after the second dose of vaccine and a subset of 12 to 23-month-old children. Given the small numbers of participants with these results, we've combined the vaccine groups here and analyzed these according to those who are RSV-naïve or experienced at baseline. It can be observed in the top row that there is a robust rise in the Th1 cytokines, interferon gamma, IL-2, and TNF-α in both RSV-naïve and RSV-experienced participants.

In contrast, for the Th2 cytokines shown in the bottom row, there was a minimal increase in IL-4 and IL-13. We do see a small increase in the Th2 cytokine IL-5 in RSV-naïve participants and in a subset of the RSV-experienced participants. Of note is that among those with detectable IL-5, the concentrations are similar amongst those who are RSV-naïve and experienced. Also, it's worth remembering that these data are displayed on a log scale and although we are seeing detectable IL-5 responses, these

concentrations are at least tenfold lower than the Th1 cytokines analyzed at a group level. This Th1 bias is also evident at an individual level. For example, this participant labeled blue with the highest IL-5 concentration also has the highest interferon gamma concentrations demonstrating a Th1 bias response in this child, and this participant is maintained across all these participants. This pattern is maintained across all these participants.

Respiratory surveillance showed no cases of RSV severe or hospitalized RSV illnesses in this age 23-month-old children up to the end of the first RSV season, the time point for the DSMB age de-escalation decision.

For these risk tables showing results of RSV respiratory surveillance here and for the rest of the presentation, we've combined both vaccine groups and compared to placebo, so the focus will be on the last two columns. Severe/hospitalized cases are shown here in yellow, showing no cases up to the DSMB review in March 2024. Therefore, the safety and immunogenicity data from 8 to 23-month-old children, nearly half of whom were RSV-naïve, supported further age de-escalation. Specifically, there were no safety concerns observed after the conclusion of a full RSV season. No severe/hospitalized RSV illnesses occurred up until the end of March 2024. And robust RSV A and B neutralizing antibodies and a preF biased binding antibody response was observed. There was evidence of the induction of a Th1 bias T-cell immune response. Together these data suggested a profile very similar to that observed in nonclinical studies in which no evidence of enhanced disease was found. This allowed age de-escalation according to WHO guidelines.

This data was shared with the DSMB who in March 2024 supported age de-escalation to 5 to 7-month-olds. Now, I've just shown surveillance data up to March for

the 8 to 23-month-old children. Surveillance has, however, been ongoing, so we'll finish this section by showing the most up-to-date results for surveillance in this age group.

Among RSV-naïve children by the time of the data cutoff in October 2024, there was one child who received the RSV/hMPV vaccine who had a severe/hospitalized RSV illness compared to none in the placebo participants. This was in a Panamanian child who was RSV-naïve at enrollment, and the case occurred in August 2024 during the second RSV surveillance season. This was 333 days after the child's third dose and after the DSMB decision to age de-escalate. The child was 2 years old at the time of the illness and had a co-infection with rhinovirus/enterovirus and was hospitalized for two days, required oxygen with therapy and made a full recovery. There were no severe/hospitalized RSV illness episodes in RSV-experienced children.

Now I'll share the results in 5 to 7-month-old children. The study progressed to Part B in which 5 to 7-month-old children received three doses of either 15 micrograms, or after a DSMB review of safety data, a dose escalation to 30 micrograms of vaccine or placebo. The study enrollment and dosing were paused on the 17th of July at which time 59 of these children had received two doses of the planned three doses of 15 micrograms of vaccine or placebo. All of these were recruited in Panama shortly before their first RSV season. We'd also recruited 21 children to receive 30 micrograms of vaccine or placebo. Twenty of these were from Panama and one was from the UK. These all received just one of the planned three doses.

Again, I will address immunogenicity first and then safety. It can be seen that two 15 microgram doses of the RSV vaccine induced neutralizing antibodies against both RSV A and B with a geometric mean fold rise of 55 and 37 respectively. Robust

responses for RSV were also seen after the combined RSV/hMPV vaccine. This is despite 88% of these children being RSV-naïve at baseline. We are just showing data for Cohorts 3 and 4, receiving 15 micrograms as we do not yet have the immunogenicity data for Cohorts 5 and 6. These children were recruited just ahead of a period of intense RSV activity and some were experiencing RSV infections between the two blood sampling time points.

This slide shows us individual level data and separates those who had a detected symptomatic RSV infection between the two blood samples and those that didn't. As can be seen, a symptomatic RSV infection in the placebo recipients resulted in a 32-fold rise in RSV A neutralizing antibodies, an increase at least matched by the 36 fold rise seen in those receiving two doses of the RSV vaccine but no detected infection. And those receiving the RSV/hMPV vaccine had a 20-fold rise. Increases in binding antibodies were seen with a 12-to-17-fold higher increase in preF binding antibodies compared to postF, representing a marked preF bias as seen in the older cohorts.

I'll now present the results of RSV surveillance in the 5 to 7-month-olds and the events leading to and following up from the dosing pause. The study dosing and enrollment were paused on the 17th of July when a second severe RSV-LRTI was identified. All dosing and enrollment were immediately stopped, the DSMB was notified as was the FDA and other international regulatory authorities in an expedited manner. From the time of the study pause, there's been very active engagement with the DSMB, the FDA and other regulatory agencies. [Indiscernible - 02:08:23] was also engaged with the investigators and have notified all parents of participants.

Respiratory surveillance and immunogenicity evaluation are ongoing despite the pause on dosing. And I'll now present the summary of respiratory cases observed up

until the 15th of October data log. Here we see the numbers of symptomatic RSV infections and severe or hospitalized RSV cases in children immunized with two doses of 15 micrograms or placebo. As a reminder, all these children were recruited in Panama. We'll look first at the RSV-naïve participants, and comparing the last two columns, among the 35 RSV-naïve children who received either vaccine 16 or 46% had a symptomatic RSV illness compared with 12 (67%) in the placebo group. Among these RSV-naïve recipients, 5 or 14% had a severe or hospitalized RSV illness compared with 1 (6%) in the placebo group. No severe or hospitalized RSV illnesses were observed in the RSV-experienced 5 to 7-month-olds. So, to summarize this slide, among RSV-naïve 5 to 7-month-olds, there is a trend to lower overall RSV infections in the vaccine groups, but higher rates of severe/hospitalized cases in the vaccine recipients versus placebo.

This slide summarizes the clinical presentations of these severe or hospitalized RSV cases. These infections occurred between June and August 2024. One case occurred between the first and second dose of vaccine and the remainder occurred up to 37 days after the second dose of vaccine or placebo. Five of these children were hospitalized and one was managed in the emergency room. Of note is that the child listed in the first row required mechanical ventilation and had a hospital admission lasting 16 days. The child's respiratory illness resolved but they are receiving ongoing treatment for arterial hypertension. All other children who were hospitalized were discharged within five days and their illnesses resolved. Two children had a co-infection, a vaccine recipient with SARS-CoV-2 and a placebo recipient with hMPV.

Here we've returned to the individual level immunogenicity data and we are showing these children who have developed severe/hospitalized RSV illness in orange. As can be seen, these children who have had two doses of a vaccine and severe or

hospitalized RSV illness ended up with very high neutralizing antibody titers. These were even higher than those induced by vaccine alone and higher than those induced by infection alone. The one severe infection in the placebo recipient happened after the second blood sample. Hence, they have no rise in antibody to show in here.

Looking now at the children immunized at 5 to 7 months with a single dose of 30 micrograms, we can see that none of these had a severe or hospitalized case of RSV illness. We are unable to classify these children as RSV-naïve or experienced as we're awaiting immunogenicity data for these cohorts.

Surveillance is being conducted for hMPV as well as RSV, and this is a preliminary report that we've had three children aged 5 to 7 months admitted to hospital with severe or hospitalized hMPV infections. Two of these occurred after two 15 microgram doses of RSV/hMPV vaccine, and one after a single 30 microgram dose of this vaccine. One of these children required respiratory support through CPAP, and the other two oxygen alone. And all children were discharged after four to nine days. We did not yet have hMPV immunogenicity results for 5 to 7-month-old children. No cases of severe or hospitalized isolated hMPV illness have occurred in the placebo or RSV vaccine recipients in these 5 to 7-month-old children.

I'll now move on to a different aspect of this study in which we evaluated the impact of prior receipt of RSV monoclonal antibody nirsevimab on the immunogenicity of the RSV vaccine. Nirsevimab is now the standard of care for providing passive protection against RSV for infants less than 8 months of age born during or entering their first RSV season in the US. And it's important to understand how nirsevimab might impact the immune response to active immunization with RSV vaccines. Our

nonclinical data suggests inhibition of RSV vaccine responses by prior administration of monoclonal antibody, which was able to be overcome by subsequent doses.

Here is the section of the study focusing on this question in which we enroll children with or without prior nirsevimab receipt with the intention to give three doses of RSV vaccine. In the end, 15 children were enrolled prior to the dosing pause, all in the US and all received a single dose of vaccine. Nine of these had had previous nirsevimab receipt and six had not. There have been no symptomatic RSV infections in these children.

Dr. El Sahly: One minute warning.

Dr. Snape: This study has shown no increase in RSV A or B neutralizing antibodies after a single dose of RSV vaccine in children who have previously received nirsevimab 6 to 9 months earlier. In contrast, in children without prior nirsevimab, we observed 60- and 19-fold increase in antibody titers for RSV A and B neutralizing antibodies respectively. As noted, nonclinical studies suggested that antibody increases in nirsevimab recipients might have been observed after the planned second and third doses, but the dosing pause was implemented before these could be administered.

Therefore, based on a small number of infants receiving prior nirsevimab, no increase in neutralizing antibodies were seen after the first dose of RSV vaccine, which suggests previous RSV antibody administration may inhibit the immune response. The potential to overcome this with subsequent doses was not able to be evaluated given dosing pause.

So, to summarize, active vaccination against RSV for children remains an urgent unmet need to provide protection beyond infancy. Moderna pursued a pediatric

development plan with its mRNA RSV vaccine based on proven efficacy of its mRNA vaccines to prevent RSV disease in older adults and SARS-CoV-2 disease in both children and adults. And the pediatric RSV development program progressed to RSV-naïve infants in accordance with regulatory guidance.

RSV-naïve infants showed robust neutralizing antibody responses with preF bias and no increase in RSV antibody after an initial dose of RSV vaccine in infants that had previously received nirsevimab. No safety concerns were identified in RSV-experienced children. However, a pause rule was triggered and enrollment and vaccination in this study stopped immediately. Active RSV surveillance allowed rapid detection of possible excess of severe or hospitalized RSV illness in RSV-naïve 5 to 7-month-old vaccine versus placebo recipients. Ongoing surveillance for RSV and hMPV infections continues. Neither nonclinical studies nor clinical studies in children 8 months of age or older predicted the imbalance of severe or hospitalized RSV disease.

Moving forward, there is no current plan to continue RSV vaccine programs in children under 2 years of age. The safety surveillance and immunogenicity evaluation will continue for children in this study. And our understanding of the clinical and immunological picture continues to evolve as we gather more data.

I'd like to take a moment to thank all the investigators, the DSMB, and the study-site personnel, and especially the children and families who participated in the studies. Thank you.

Joining us today are three external experts to help address any questions you may have, all of whom are pediatricians. Dr. Edwards is our DSMB Chair. Dr. Ramilo is an expert in RSV immunology. Dr. Sáez-Llorens is the Principal Investigator for our study in Panama. Thank you.

Review of Investigational RSV (mRNA-1345) and RSV/hMPV (mRNA-1365) Vaccines in Infants and Children < 2 Years – Q&A

Dr. El Sahly: Well, thank you, and I would like to invite the team to use the raise-their-hand function for questions. And we begin with Dr. Gans. And given that we only have 10 minutes now for Q&A, if you don't mind keeping your questions to the point and commentary. And additional questions will be asked in the discussion portion. Thank you. Dr. Gans.

Dr. Gans: Thank you, Hana and thank you, Dr. Snape. I may have missed this. So, just two quick clarifying questions for conversation later. In the combined RSV and the human metapneumo virus, which was marked at 30, is that 15 of each of them or 30 of each of those antigens?

So, that was one question. My other question for you is in those severe diseases I saw the antibody responses, the humeral responses, I didn't actually see the cell-mediated responses in those to see if they actually varied at all from those who didn't have severe disease. So, I may have missed that data. I also didn't see CD 4 versus CD 8.

Dr. Snape: Okay, so three questions. The answer to the first question is a 30 microgram dose of the combined vaccine contains 15 micrograms of each component. The answer regarding the cellular immune response in the children who became sick in the 5 to 7-months-old, what I've shown you is CMI data in the older cohort, the 8 to 24-month olds, and that was in a subset of the 12 to 24-month-old children there. None of those children became severe or severely unwell or hospitalized in those children that we have CMI data for. We are obtaining CMI data for the 5 to 7-month olds, but we

don't have that data to show you today. And can you remind me of your last question? Sorry, Dr. Gans.

Dr. Gans: Sorry, I didn't see in your cellular data if you actually looked at CD 4 versus CD 8. I saw the cytokine profiles.

Dr. Snape: No, we were just able to look at the cytokine profile given the small volume of blood that we were able to obtain in these children.

Dr. El Sahly: Thank you. Next I see Dr. Portnoy. Before Dr. Portnoy's question, I want to make sure that all of the Moderna colleagues will be available because there's going to be a plethora of questions and your presence is crucial.

Dr. Portnoy: Great, thank you. Just two quick questions. Number one, I'm trying to understand the long-term goal of this plan, is the plan to give passive immunization to newborns and then start active immunization at 5 to 6 months? Or are we planning to actually go down and give newborns the vaccine? And if patients do get the vaccine, are they less likely to transmit it to other people as they are in a carrier state that occurs? And is that prevented by the vaccine? Do you have information about that?

Dr. Snape: To be clear, we're not planning to progress this program further in the under 2-year olds. So, we are not planning any further age de-escalation or in any dosing in this age group. We did want to assess the interaction with nirsevimab given [that] I think that will be important for any vaccine programs going forward to work out how it might interact. But yeah, as I said, we would not be doing further progression of that onto a 2-year-old program. And I do agree it would be--

Dr. Portnoy: [Indiscernible 02:20:43] carrier. Yeah, go ahead.

Dr. Snape: I do agree it would be interesting to assess the possibility that vaccines might reduce transmission, but we hadn't got to that step in the program before we have paused, as I say, for the progression in other 2-year-olds.

Dr. Portnoy: And one other question. The infants who did have the severe disease and were hospitalized, were there any risk factors for those infants that differentiated those from the ones who weren't hospitalized other than getting the vaccine or not? Like, did they have atopic dermatitis? Was there a family history of allergy? Were they predisposed to a Th2-type of response?

Dr. Snape: So, just to look at these children, again, I can tell you that all children were-- The inclusion-exclusion criteria were very sick. These children did not-- Were very strict. These children did not have underlying conditions. They were all born at term. They did not have any history of wheezing or any individual concerns at that level. And I'll actually bring in Dr. Sáez-Llorens if he wants to further comment about the medical history of these participants.

Dr. Sáez-Llorens: Yes, hello to everybody. They were previously healthy infants and the exclusion criteria were very clear in not to enroll those patients with risk factors.

Dr. Portnoy: Okay, thank you.

Dr. Snape: I'm just showing here quickly again, sorry, the inclusion-exclusion criteria that we used for this study. Thank you

Dr. El Sahly: Dr. Paul Offit.

Dr. Offit: Yeah, thanks Hana. So my question is, given that you have a vigorous preF response for this vaccine, what are you postulating? Is the immunological

mechanism by which these children suffered severe disease in the vaccinated group, or do you think you were just unlucky and that there were two children that just happened to have severe disease and the numbers are small?

Dr. Snape: The numbers are small. We agree. It was clear that there was a trend here that meant that we couldn't progress further dosing and enrollment. I think that was the right decision, but the numbers are small. We've not found the likely mechanism of action for these findings if they're confirmed. And we're gathering more data to understand these findings and we'll be sharing the data with the public as it becomes available. And we welcome the input of VRBPAC today for suggestions of possible further research to elucidate mechanisms of action, and we'll be engaging with the broader scientific and regulatory community to understand these results.

Dr. Offit: Thank you.

Dr. El Sahly: A lot of suggestions during the discussion portion. Dr. Monto.

Dr. Monto: My concern is drawing a conclusion about the presence of antibody, the numbers as I watched going by in Cohorts 3 and 4 that had prior antibody was, I think, five or six. So, you really can't conclude about antibody being protective. The other thing that is interesting to me is that as I saw the data going by, the challenge with the hMPV also produced severe disease. Was I correct in that?

Dr. Snape: Can I clarify the first question? Are you talking about the children who received prior nirsevimab monoclonal antibody?

Dr. Monto: No, I'm talking about the study in Panama, Cohort 3 and 4.

Dr. Snape: Cohort 3 and 4. Thank you very much. We enrolled 60 children there. Twenty received the RSV vaccine and 20 received the combination RSV/hMPV vaccine. And you can see here on the right, actually at an individual level, the numbers of children. So, there were 16 that received the vaccine with no infection between the two blood sampling time points, and we saw a robust increase in antibodies for those 16 children. Overall, the antibody increase was 36 fold compared to 32 fold after the natural infection in the placebo participants shown on the left side. And we also saw the similar-- We did see an increase also in the 12 RSV/hMPV recipients that you can see here. Does that answer that question, Dr. Monto?

Dr. Monto: Are you distinguishing between those who have had experience before infection? Because there was another table which separated them out.

Dr. Snape: Yes. So, in this cohort, in the 5 to 7-month olds, of the 60 children, 53 were considered RSV-naïve, only six had prior infection.

Dr. Monto: It's among those six.

Dr. Snape: So, those six. The numbers are small, absolutely, but we did not see any severe disease in those.

Dr. Monto: Well, but with that kind of number, can you conclude that prior infection is protective?

Dr. Snape: No, but we did have more in the 8 to 24-month-old children. We recruited 90 children and 42% were naïve. And again, we've really not seen the same signal in that age group, in the naïve or RSV-experienced cohorts in the older children.

Dr. Monto: And you are seeing a triggering of severe disease with hMPV infection. Is that true?

Dr. Snape: Preliminary data here, I'm just bringing up again. There were three children in Panama who have been hospitalized with hMPV infection. The RSV infections were occurring, of course, during the RSV season running from June to August especially. We're now in an hMPV season in Panama, and we have seen three children hospitalized with hMPV infection between September and December. You can see the dosages and the timings outlined here. All of these children fortunately recovered. And so, that's three children, all in the RSV/hMPV combination vaccine. And we've not seen severe cases in those that received either RSV or placebo.

Dr. Monto: So, the situation is even more complicated than RSV. Thank you.

Dr. El Sahly: Yeah, 3 out of 27 hMPV is huge. A question pertaining to the immune response, did the team look at IgG isotypes with emerging data that potentially the mRNA platform has a, I guess, tendency or to cause elevated IgG four, at least with the SARS-CoV-2 to insert?

Dr. Snape: We will be looking at the subtypes we haven't done yet. We haven't done those data yet. Yep.

Dr. El Sahly: Okay. And I noticed also when it comes to the immune response that whenever hMPV is given with the RSV, the RSV responses were much lower. So, is my interpretation correct? Is there antigenic interference potentially when the two are given together?

Dr. Snape: I think it comes down to the first question, which is to say that in a 30-- For example, let's say a 15 microgram dose of RSV standalone, you have 15

micrograms of RSV. In a combination vaccine, you have only 7.5 micrograms of RSV. And so, that is-- We have a lower dose of RSV.

Dr. El Sahly: A lower dose, a lower dose. That makes sense. Thank you. So, I'm sure a whole lot more questions, but thank you for presenting those data today. So, now on the agenda, we have a quick five-minute break. It is 10:57. We will reconvene at 11:03 for the presentation, 11:03, by the FDA. Thank you.

FDA Presentations

Imbalance in Severe Respiratory Syncytial Virus (RSV) Cases in a Clinical Trial of an RSV vaccine in Infants and Young Children

Dr. El Sahly: Welcome back from the very short break. I would like to introduce now from the Division of Clinical and Toxicology Review, Dr. Mark Connelly. Dr. Mark Connelly is Team Leader Clinical Review Branch 3 at CBER in the FDA. He will go over the imbalance in severe RSV cases in a clinical trial of RSV vaccine in infants and young children and the implications for pediatric RSV vaccine development. Dr. Connelly?

Dr. Connelly: Yes, good morning. My name's Mark Connelly and I'm a Team Leader in the Division of Clinical and Toxicology Review in the Office of Vaccines Research and Review. And today I'll be discussing an imbalance in severe and hospitalized RSV cases observed in a clinical trial of an RSV vaccine in infants and young children and its implications for clinical development of pediatric RSV vaccines. Next slide, please.

This is an outline of the topics that I'll cover in my presentation today. First, I will provide an overview of pediatric RSV vaccine development including a brief summary of the unmet need for RSV vaccines in children, RSV vaccine-associated

enhanced respiratory disease, the 2017 VRBPAC meeting and result in study design considerations for RSV vaccine trials, and an overview of RSV vaccines development. Next, I will discuss the imbalance in severe/hospitalized RSV cases observed in one clinical trial of an RSV vaccine in infants including clinical details and preliminary immunogenicity data from the study. I will then provide a brief summary of cases of severe/hospitalized human metapneumovirus infection noted in the same study. This will be followed by a summary and list of considerations for pediatric RSV vaccine development. And finally, I will review the topics for discussion today with VRBPAC. Next slide, please.

I'll start with a brief review of the unmet need for RSV vaccines in children. Next slide, please. As discussed by earlier speakers, there's a large global burden of RSV disease. Children in low and middle-income countries and those under 6 months of age are especially impacted. The risk of RSV infection is age-dependent with approximately 53% of US infants infected by 1 year of age. Almost all children are infected at least once by 3 years of age. Although there may be epidemiologic and regional differences that affect seroprevalence, RSV infection does not confer long-lasting protection and reinfection is common.

While adults have active RSV immunization options available, there are no such vaccines that are FDA-approved for use in those under 18 years of age. Passive immunization platforms are the only currently available preventative options for children. Examples include monoclonal antibodies like nirsevimab and maternal immunization. These passive immunization options have greater availability in high-income countries than in the low and middle-income countries most impacted by RSV disease. Active immunization may offer additional benefits for children including more available RSV preventative options, immune priming to provide protection to

vaccinated individuals in subsequent RSV seasons, vaccination of children in subsequent RSV seasons, a vaccination option for children whose mothers received maternal immunization during the prior pregnancy. RSV vaccine-associated enhanced respiratory disease has necessitated specific risk mitigation measures to protect participants during the pediatric development of RSV vaccines. Next slide, please.

RSV vaccine-associated enhanced respiratory disease, abbreviated as VAERD, is defined as severe lower respiratory tract disease due to wild type RSV infection that occurs at a higher frequency following immunization with an RSV vaccine when compared to the frequency seen among those given a controlled vaccine. This was observed in the 1960s when RSV-naïve children who'd been vaccinated with a formalin-inactivated RSV vaccine developed severe cases of RSV lower respiratory tract disease with natural RSV infection. These cases mostly occurred during the participants' second RSV season. As discussed by Dr. Piedra, features of the formalin-inactivated RSV vaccine and associated RSV VAERD include absent preF antigen in the formalin-inactivated RSV vaccine, low avidity or inadequate neutralizing antibody responses to vaccination, unbalanced T-cell priming following vaccination with a Th2-biased $CD4^+$ T-cell response, cytokine-mediated pulmonary injury with RSV infection after vaccination. VAERD was not observed in children who were RSV-experienced prior to vaccination. Subsequent pediatric RSV vaccine development has been informed by research evaluating the immune responses to the formalin-inactivated RSV vaccine and VAERD pathogenesis. Next slide, please.

With advances in vaccine technology and understanding of the mechanisms of VAERD, there's been renewed interest in filling the unmet need for pediatric RSV vaccines. Accounting for the history of VAERD following formalin-inactivated RSV vaccination, a VRBPAC meeting was convened on May 17th, 2017, to provide

recommendations to facilitate future pediatric RSV vaccine development. Consensus recommendations from this meeting included that nonclinical data should distinguish immune responses to candidate vaccines from those elicited by the formalin-inactivated RSV vaccine prior to study in RSV-naïve children. Clinical study designs should include specific criteria to identify potential enhanced respiratory disease cases as severe RSV disease may develop in a percentage of unvaccinated individuals. And while nonclinical data and clinical data from RSV-experienced populations may support vaccine evaluation and participants are likely to be RSV-naïve, close and continuous monitoring for VAERD is essential during clinical studies of RSV vaccines other than live-attenuated RSV vaccines and children who are likely to be RSV-naïve. Next slide, please.

As a result of these VRBPAC recommendations, the FDA requires nonclinical and clinical safeguards to mitigate the risk of VAERD for any sponsor seeking to evaluate an RSV vaccine candidate other than a live-attenuated RSV vaccine in children who may be RSV-naïve. Nonclinical data from animal models should demonstrate that the candidate vaccine expresses or presents prefusion epitopes of the RSV antigen, induces robust anti-RSV neutralizing antibody responses while avoiding induction of non-neutralizing antibody responses as evidenced by relatively low anti-RSV F IgG binding to neutralizing antibody ratios, avoids induction of strong Th2-type $CD4^+$ T-cell responses, and does not provoke pulmonary injury in a valid RSV-challenge model. These nonclinical data are reviewed by the FDA prior to initiation of clinical studies. In addition to these nonclinical measures, clinical safeguards are of the utmost importance to allow for early detection of potential VAERD cases during the evaluation of a candidate RSV vaccine. Next slide, please.

Safeguards for clinical studies of RSV vaccine candidates include age de-escalating study designs, restriction of study populations to healthy children without conditions that increase the risk for severe RSV disease, study designs that provide safety and immunogenicity data from presumed RSV experience participants during an RSV season, support studies in presumed RSV-naïve infants and children, adequate study pause rules and pre-specified RSV case definitions to aid in the detection of a safety signal suggestive of VAERD, and use of Data Safety Monitoring Board or Data Monitoring Committee for ongoing review of study data to identify potential safety signals, and provide recommendations for pausing study enrollment to allow for safety review. Additional recommended measures include collection of immunogenicity data to evaluate both humoral and T-cell responses to vaccination, and determination of baseline serostatus to inform interpretation of safety data. Next slide, please.

These safeguards have facilitated the development of a variety of RSV vaccine platforms. There are currently 26 candidate RSV vaccines with pediatric clinical development programs under U.S. IND. While 15 of these are live-attenuated RSV vaccines, 11 use other vaccine technologies that include an RSV F glycoprotein antigen stabilized in the preF confirmation expressed as recombinant protein or encoded by mRNA. Using the recommended clinical safety monitoring measures, an imbalance in severe RSV cases in RSV-naïve infants has been identified in one clinical study of a candidate mRNA vaccine. Next slide, please.

I will now present an overview of the study in which the imbalance in severe/hospitalized RSV cases was observed. Prior to clinical study initiation, nonclinical data were reviewed and were reassuring to mitigate the risk of VAERD. Next slide, please.

Parts A and B of this Phase I study were designed to evaluate a three-dose schedule of an RSV-only vaccine and an RSV+hMPV combination vaccine as compared to a single placebo. The study also included an open-label Part C that evaluated the RSV-only vaccine, nirsevimab-exposed and unexposed participants. The clinical study design incorporated the recommended safeguards to mitigate the risk of VAERD, including a study population restricted to healthy children without permission that increased the risk of severe RSV disease. Study initiation in older participants more likely to be RSV-experienced (study Part A) reviewed safety and immunogenicity data through an entire RSV season prior to enrollment of younger participants more likely to be RSV-naïve (study Part B). Prespecified RSV case definitions and stopping rules to allow for the evaluation of potential imbalances in RSV cases, a DSMB to review safety data and provide recommendations to protect study participants and to support age de-escalation, study endpoints evaluating immune responses to vaccination, and determination of baseline serostatus to inform interpretation of safety signals. Safety monitoring measures in this study identified two cases of severe/very severe RSV lower respiratory tract infection that led to a pause in study enrollment and dosing. Next slide.

On July 17th, 2024, the sponsor was made aware of two RSV cases meeting the protocol definition of severe and very severe RSV lower respiratory tract infection in Part B Cohorts 3 and 4. All dosing enrollment in study Parts B and C were paused. Participants continued to be followed for safety in RSV case surveillance. At the time of the study pause, Part B Cohorts 3 and 4 were fully enrolled and participants had received two of three study doses. Part B Cohorts 5 and 6, and Part C were enrolling, and participants had received one study dose. The DSMB was convened for an ad hoc meeting and recommended continued study pause. The FDA was notified of the study pause and the IND was placed on clinical hold. A partial hold on enrollment of children

less than 2 years of age and RSV-naïve children 2 years to less than 5 years of age was implemented for all pediatric studies under U.S. IND with the exception of studies using live-attenuated RSV vaccines.

The sponsor at the DSMB's recommendation established a blinded clinical assessment team to monitor for additional cases of significant RSV disease and a postdoc definition for cases of clinically significant severe/very severe lower respiratory tract infection, which I'll refer to hereafter as severe/hospitalized RSV cases, was established to better identify RSV cases of interest. This case definition included any RSV case that met the per-protocol definition of severe RSV lower respiratory tract infection, very severe RSV lower respiratory tract infection or that required hospitalization. Additional severe/hospitalized RSV cases have been identified in Part B Cohorts 3 and 4. Next slide, please.

This is an overview of the cases of RSV disease reported across all study parts and cohorts through a date of data cutoff, November 18th. The left-hand column represents the study part and cohort. The second column is the vaccine dose. The third column shows the number of symptomatic RSV cases and the percentage of the total number of participants receiving the indicated vaccine in the cohort. The fourth column shows the number of severe/hospitalized RSV cases and the percentage of the total number of participants receiving the indicated vaccine in the cohort. The fifth column reports the percentage of symptomatic RSV cases that progressed to severe/hospitalized RSV cases. Part A had one reported severe/hospitalized RSV case and a combined RSV+hMPV vaccine recipient. This case occurred in the second RSV season after enrollment of Part B participants had begun. Part B Cohort 3 had two reported severe/hospitalized RSV cases among RSV-only 15 microgram recipients. Part B Cohort 4 had three reported severe/hospitalized RSV cases among combined

RSV+hMPV recipients. There was one severe/hospitalized RSV case among Part B participants in Cohorts 3 and 4 who were placebo recipients. For those cases that progressed to severe/hospitalized RSV cases, these represented 22% of symptomatic RSV cases and the RSV-only vaccine recipients Cohort 3, 30% of symptomatic RSV cases in combined RSV plus human metapneumo virus recipients in Cohort 4, and this was as compared to 8% of symptomatic RSV cases in placebo recipients. Next slide, please.

This table displays the imbalance in severe/hospitalized RSV cases among RSV-only and RSV+hMPV combination vaccine recipients. This is shown combined as compared to placebo recipients. The combined percentage of symptomatic RSV cases in vaccine recipients in Cohorts 3 and 4 that progressed to severe/hospitalized RSV cases was 26% as compared to 8% of placebo recipients. Next slide, please.

This provides a clinical overview of the severe/hospitalized RSV cases in Cohorts 3 and 4. All participants in Cohorts 3 and 4 who developed severe/hospitalized RSV cases were generally healthy. Cases among vaccine recipients occurred a median of approximately 12 days after study dose two with a range of three to 26 days. One case occurred 23 days after dose one. The case in the placebo recipient occurred 37 days after dose two. Local RSV epidemiology may have played a role in timing of these cases relative to the study dose. Four of the five events in vaccine recipients required hospitalization with one participant requiring ICU admission. Three of the five vaccine recipients required some form of respiratory support with two requiring nasal cannula and one requiring intubation in mechanical ventilation. The placebo recipient was hospitalized and required nasal cannula as respiratory support. SARS-CoV-2 infection was detected in one of the vaccine recipients. This was not the participant who required mechanical ventilation. Human metapneumo virus co-infection was detected in the

placebo recipient. The median time to event resolution was 19.5 days with a range of 8 to 31 days. Next slide, please.

I will now discuss some preliminary immunogenicity results starting with study Part A. As a reminder, there is no imbalance observed in RSV cases in this study part and these are preliminary data from Phase I study. There's limited ability to draw conclusions from these results. Next slide.

Preliminary immunogenicity data from Part A demonstrated that 45% to 65% of participants were seropositive at baseline using the post-talk definition of a postF IgG binding antibody concentration greater than or equal to 200 AU/mL. Looking at the neutralizing antibody binding antibody responses at day 85, which were measured approximately 28 days after study dose two. These responses were greatest among RSV-only vaccine recipients and least among placebo recipients. Measurements of cytokines representative of T-cell responses were available for a small subset of Part A participants. This subset did not include the Part A participant who developed the severe/hospitalized RSV case.

Preliminary analysis of these data suggest that at baseline participants defined as RSV-experienced have quantifiable Th1 cytokine responses measured by IL-2 interferon gamma and TNF-α. The Th2 cytokine responses by IL-5, IL-13 and IL-14 were below the lower limit of quantification. For vaccine recipients, both RSV-naïve and RSV-experienced participants had generally similar Th1 responses. An observation from the Th2 cytokine responses includes a potential trend towards a greater proportion of participants defined as RSV-naïve having measurable IL-5 responses as compared to participants defined as RSV-experienced. Although the magnitudes of the IL-5 responses were low relative to responses reported for other vaccines, the significance of

this observation is not clear. Other Th2 cytokine responses IL-13 and IL-4 were similar between groups. Placebo recipients, including those defined as RSV-experienced, had 85 Th2 cytokine responses below the lower limit of quantification. The ability to draw conclusions from these preliminary T-cell immunogenicity observations is limited given the small numbers of participants per group with available data and the lack of T-cell data from participants with severe RSV disease. Next slide, please.

Preliminary immunogenicity results from the cohorts in which the imbalance was observed, Part B Cohorts 3 and 4, are available for humoral immune responses only. Next slide, please.

Samples again were collected in these cohorts at baseline and at study day 85 approximately 28 days after dose two. RSV infections may have occurred prior to the day 85 immunogenicity sample collection, which may confound the interpretation of the immunogenicity results. Of four vaccine recipients who went on to develop severe/hospitalized RSV cases, the RSV event occurred prior to the day 85 sample collection. One participant in this group did not have a day 85 sample collection. For the placebo recipient, RSV infection occurred after the day 85 sample collection.

Preliminary data evaluating neutralizing antibody and binding antibody responses at day 85 demonstrated the highest responses among those participants who developed severe/hospitalized RSV cases and the lowest responses among placebo recipients. These preliminary immunogenicity data suggest differences in the severe/hospitalized RSV cases as compared to VAERD cases after the formalin-inactivated vaccine, but characterization of the immune responses of these participants is not complete. Determination of baseline serostatus was likely confounded by the presence of maternal-derived antibodies as all participants were seropositive using the

protocol definition of a neutralizing antibody titer greater than or equal to the lower limit of quantification. As noted earlier by Moderna post hoc exploratory analysis conducted by the sponsor suggests that all participants in these cohorts that develop severe/hospitalized RSV cases were seronegative at baseline. Next slide, please.

Preliminary immunogenicity results are also available from study Part C. Again, no imbalance in RSV cases was noted in this part. Next slide, please.

Preliminary immunogenicity data from Part C participants demonstrated potentially blunted responses to a single 30 microgram dose of RSV-only vaccine administered to nirsevimab-exposed participants. This was especially for the RSV B responses as highlighted in the box below. Of note, measurements following the complete three dose series are not available due to the study pause. Next slide, please.

I will also review some early data regarding severe/hospitalized human metapneumo virus cases observed in this study. Next slide, please.

Severe/hospitalized cases of human metapneumo virus were identified in participants in study Part B. Two combined RSV+human metapneumo virus vaccine recipients in Cohort 4 had severe/hospitalized cases of hMPV. One participant required noninvasive respiratory support in the form of continuous positive airway pressure (or CPAP). One combined RSV+human metapneumo virus vaccine at the 30-microgram dose level. The recipient that received this in Cohort 6 had a severe/hospitalized case of human metapneumo virus infection. This case was reported to FDA after the briefing document was finalized and so, it's not reflected in this document. As mentioned earlier in the presentation, there was one severe/hospitalized RSV case and a placebo recipient that also had an hMPV co-infection. Again, these are preliminary data and the investigation of these cases are ongoing. Next slide, please.

I'll now summarize the findings from the study in which an imbalance in severe/hospitalized RSVcases was observed and described potential considerations for pediatric RSV vaccine development. Next slide, please.

In one clinical study, a numerical imbalance in severe/hospitalized RSV cases was observed in children 5 months to less than 8 months of age who received an RSV-only vaccine or combination RSV+human metapneumo virus vaccine as compared to placebo. Nonclinical and clinical safeguards were in place for this study based on our understanding of VAERD following the formalin-inactivated vaccine. The mRNA vaccine construct was designed and non-clinical data were assessed prior to the clinical study to mitigate the risk of VAERD.

Preliminary immunogenicity data suggest differences in the severe/hospitalized RSV cases observed in this study as compared to formalin-inactivated RSV VAERD cases. Again, characterization of these cases is not complete. The implication of the observed imbalance for other pediatric RSV vaccine programs are uncertain. The partial hold on enrollment of children less than 2 years of age and seronegative individuals 2 through 5 years of age remains in place for pediatric clinical development programs for RSV vaccines under U.S. IND other than live-attenuated RSV vaccines. Next slide, please.

Considerations for enrollment of presumed RSV-naïve infants and children for RSV vaccine candidates under U.S. IND include: 1) if and how our current understanding of the formalin-inactivated RSV-vaccine associated enhanced respiratory disease pathophysiology may form benefit-risk assessments of other vaccine technologies; 2) what critical additional assessments may help further characterize the observed safety signal in the study discussed today; 3) what additional data may help

stratify potential VAERD risk across vaccine technologies and antigenic compositions; 4) how nonclinical studies may further inform potential VAERD risk in clinical studies; 5) what additional risk mitigation/management strategies may address potential VAERD risk in clinical studies; 6) how the benefit-risk assessments may incorporate vaccine candidate benefits in RSV-experienced children, uncertainties regarding potential VAERD risk, and available preventative interventions (for example, RSV monoclonal antibodies and maternal immunization); and 7) how to address potential RSV monoclonal antibody or RSV vaccine interactions in clinical development plans and pediatric clinical study designs. Next slide, please.

I'll now present the discussion topics for today's VRBPAC meeting. Next slide, please. The first topics for discussion relate to RSV vaccine safety and pediatric populations, and include: 1.1) Please discuss whether the currently available evidence indicates a potential safety concern more broadly applicable to the evaluation of RSV vaccine candidates in infants and toddlers. Please discuss the applicability to: a) different vaccine technologies (for example, live-attenuated RSV, viral-vectored, mRNA, and subunit protein vaccines); and b) different antigenic confirmations (for example, stabilized preF or other RSV protein prototypes).

1.2) Based on the currently available evidence, please discuss current nonclinical and clinical safeguards, and recommend whether any additional nonclinical and clinical information should be considered and/or precautions taken when evaluating RSV vaccine candidates in infants and toddlers. Next slide, please.

The next topics for discussion relate to the sequential administration of RSV monoclonal antibodies followed by RSV vaccines in infants and toddlers and include:

2.1 Please discuss whether currently available evidence suggests potential RSV monoclonal antibody (for example, nirsevimab) - RSV vaccine interactions that may affect active immunization in infants and toddlers.

2.2 Based on currently available evidence, please discuss and recommend whether any additional factors and data should be considered when evaluating RSV monoclonal antibody - RSV vaccine interactions including potential impact of administration of RSV monoclonal antibodies on safety and/or effectiveness of subsequent parenteral or mucosal administration of RSV vaccines.

Next slide, please. I will now welcome your questions and comments. Thank you.

Imbalance in Severe Respiratory Syncytial Virus (RSV) Cases in a Clinical Trial of an RSV vaccine in Infants and Young Children – Q&A

Dr. El Sahly: Thank you so much, Dr. Connelly. Please use your raise-your-hand function to ask questions to Dr. Connelly. And we begin with Dr. Berger.

Dr. Berger: Thanks, Dr. Connelly, for a really clear presentation. Much appreciated. I'm actually curious, you mentioned that there were 26 development programs that were ongoing, 15 are live-attenuated, and the other 11 are either recombinant or mRNA. I'm curious if you've actually evaluated any of the other development programs to see if they're having similar results to what we're hearing today. Thanks.

Dr. Connelly: As of today, we have not been notified of anything in the other development programs, but of course we are monitoring and in contact with them as well.

Dr. El Sahly: Thank you. Dr. Meyer.

CAPT Meyer: Thank you as well for that presentation. I have, maybe a somewhat similar, but different question as Dr. Berger. So, I was just thinking about the safeguards that were put in place for these studies, both in preclinical and clinical safeguards, and presumably all of the trials that have been ongoing, including the Moderna one, they all have met these safeguards, but we're still seeing this signal with Moderna. So, I'm wondering if we have any more information from the preclinical stage of any studies or any candidates that did not make it past the preclinical stage. So, for example, Arexvy, which is only licensed in older adults, there's language in the package insert that says "Animal model suggests that this wouldn't be safe for children under the age of 2" due to animal models that suggest a risk. So, I guess my question is: Are there other preclinical studies that have been done that didn't make it past the safeguards? And can we use any of the information gleaned from those to help us figure out what might be going on with the Moderna candidate that made it past the safeguards, but we're still seeing this signal? Hopefully my question made sense so it's clear.

Dr. Connelly: Yes, thank you for that question. I'm going to defer that answer to Dr. Judy Beeler.

Dr. Beeler: This is Judy Beeler, Division of Viral Products. My first VRBPAC meeting was on enhanced disease for RSV vaccines, and that was a closed session for a product that had been tested in cotton rats and mice, and the testing was inadequate at the time. I'm not going to go into details because, as you know, a lot of this information is proprietary, but that was the first example. So, I've been here a while, so we are going back decades. And so, that was the first time. And then other vaccines, I think some

vaccines are tested, and the sponsors don't submit that data because they know what our response will be. So, I'm sure that there are nonclinical data out there, and the sponsors have done self triage and not submitted it to the agency. In terms of the GSK, that's also non-proprietary data, and I can't speak to it. But one would think that-- I know that MedImmune published data testing both preF and postF with adjuvants that skewed response to either Th1 or Th2-type responses, in a dose de-escalation study in cotton rats, and their data demonstrated that either preF or postF antigen could elicit enhanced disease in cotton rats.

CAPT Meyer: Thank you.

Dr. El Sahly: Thank you. That last point Dr. Beeler mentioned is sort of the confusing-- Or at least the one piece of information that sort of casts a shadow over the predictability of models. It's like if you tweak the antigen or the adjuvant slightly enough, you will trigger that particular phenotype in an animal model and its implications for humans is really confusing. Dr. Janes.

Dr. Janes: Thank you. I had a question I guess initially for the FDA. Both the FDA presentation and Moderna's presentation took care to point out that the primary endpoint of the trial, I gather, did not include severe LRTI, very severe LRTI and hospitalization as criteria for a primary endpoint event whereas, I gather, once the safety signal was identified, the endpoint definition was broadened to include those more severe outcomes. And I guess I'm wondering if the FDA can start on helping understand why those more severe outcomes were initially not included in the primary endpoint and what the thinking is for particularly safety monitoring around other vaccine platforms going forward. Thank you.

Dr. Connelly: So, to clarify-- And again, I can also allow Moderna to speak to this later too. But there were protocol-specified definitions of severe and very severe LRTI. The post hoc definition of the clinically significant severe/very severe LRTI was established to cast a broader net to make sure that any cases contributing to the potential balance were detected. So, the study was designed to evaluate each of those different definitions other than the post hoc definition I just mentioned, and then that post hoc definition was included to make sure that we got the most accurate portrayal of a potential imbalance.

Dr. Janes: Okay.

Dr. El Sahly: Dr. Gans.

Dr. Gans: Thank you once again. Thank you for that, again, review of the data. Once again, my question relates to-- I think what other people are getting at is we're trying to evaluate other platforms and just reflecting on experiences we have again with another formalin-inactivated vaccine that then subsequent which had enhanced disease and then subsequently we have a very effective live-attenuated vaccine and measles. Are people collecting the immune response to these live-attenuated platforms that are being evaluated for RSV? You outlined several live-attenuated vaccine platforms that are under development. And what is happening with it? Do we have any information? I realize you don't have the signal of enhanced disease, which is wonderful and I have to applaud Moderna for bringing this all forward, but I'm wondering if you have any data on other platforms in terms of some of these other markers that we're looking at.

Dr. Connelly: So, I think to answer your question-- Thank you for that. The Open Public Hearing will include some presentations on some of this other data. Again, much of this is proprietary, so I won't be able to discuss it here, but stay tuned for some of those presentations.

Dr. El Sahly: Dr. Kotloff.

Dr. Kotloff: Yes, thank you, Hana. And thank you for these beautiful presentations. I've learned a lot. I think one thing, one observation that's really striking me, and it sounds like other members, is that all of the guardrails that we had in place did not predict whether or not the severe outcome was going to occur. And so, I'm trying to look and see what we have left to look at, and one is that it does seem that perhaps the presence of maternal antibody may be protecting against these responses. It looked like of the three Group B children who had severe disease, that two of them had rather low baseline antibody levels. And I think it might be interesting to incorporate into the preclinical models mice that were vaccinated to see whether there's a difference in when you vaccinate the offspring if there's protection with maternal antibody in the animal models.

And I think that we also at this point can't say I don't think with confidence that live-attenuated vaccines are safe for sure. So, if we go back to the measles model, the problem with measles is that it's ineffective for the first 12 months of life, especially when you have a population that's had natural immunity. And so, you don't really get a good sense of the safety of the vaccine because you can't really give it till maternal antibody is gone. And in the US that typically used to be around 12 months of age, maybe it's waning a little bit sooner. And so, I do feel like we can't say with complete confidence that we have enough information to know, unless there is enough experience with RSV live-attenuated vaccines to say that. I'm not sure that we have enough information to know what parameters to use.

And then the other thing, I think we're very focused on weaknesses and what the gaps are, but I do think that the monoclonal antibody has performed unbelievably well

and actually can address both of those weaknesses if you give a dose in the first and second year of life. And I also don't know for sure whether there's interference with vaccine responses, because those who got nirsevimab had such high baseline levels that it was hard to see a fourfold rise when you start out so high. And so, I'm not sure that we can conclude now that that is a prohibiting factor. And I do think that one important development pathway that we should be focusing on are affordable monoclonal antibody formulations. I know that Gates MRI was involved in developing one of those. I don't know where that stands, but I just didn't want that to get lost in the desire to have a vaccine even though I am a vaccinologist and that's always my preference. In this case, the monoclonal antibody has really performed very well. Thank you.

Dr. El Sahly: Thank you, Karen. As a corollary to that, the landscape of the unmet needs is evolving and that will have a huge implication to the risk-benefit ratio of what we study in the future as well. Dr. Nelson.

Dr. Nelson: Thank you very much. I want to say thank you again for such a clear presentation really all this morning. My question really surrounds the timing of the day 85 blood draw of which we are expected to make some inferences with respect to vaccine immune responses as potential risk for these severe infections that were observed at variable times before the actual blood draw. So, can you give me a better sense as to how much earlier the four recipients who experienced the severe reactions had their events before that day 85 blood draw? And is there any shareable data regarding the immune status at the time or during the infection and treatment? We're a little worried about what treatments they received as part of their infection modulating some of the immune response and if we're basing our assessment of their response post immunomodulatory treatment, it should impact our interpretation. Thank you.

Dr. Connelly: Thank you for your question. The timing we agree on is important in terms of the exact numbers. I'm going to defer that answer to Moderna because they have that data. It's their data and so they'll be able to give you the most informed answer.

Dr. El Sahly: Do we have a Moderna team member available?

Dr. Nelson: We can wait till this afternoon if that's preferable.

Dr. El Sahly: Here we go.

Dr. Snape: I can respond to that if you'd like. And can I actually ask the team to bring up our sixth slide where we can look at this in the timing of immunizations so you get a sense of timing of infections related to immunizations? Okay. Anyway, firstly we'll look at this slide, which just reiterates that yes, some of the children that had the immunogenicity assessments both at baseline and day 85 did have infections. The infections we observed-- Four of the five infections in vaccines recipients came within 23 days with the second vaccine. So, they were occurring anytime from three days after the vaccine to 23 days. So--

Dr. Nelson: How many days is that before the day 85 draw?

Dr. Snape: The 85 blood draw was done at around day 28.

Dr. Nelson: Okay.

Dr. Snape: Around two to three injections. In terms of immunomodulatory therapies, it's possible some of these children receive steroids. As you can see-- I mean, these children had very high antibody titers. This is the slide that we can see at the moment. These are very high neutralizing antibody titers that were observed.

Dr. Nelson: Yeah, I don't think it would impact significantly the neutralizing antibody response, but we're putting a lot of weight on the Th1 versus Th2 response and I think it could affect that. That was the nature of my question.

Dr. Snape: I understand. Fine. We haven't obviously got the Th1, Th2 results in these children. We are collecting and assessing PBMC results in these children. We don't have those data yet, but we'll take that into account. Thank you very much.

Dr. El Sahly: So, Dr. Snape, the Th2 response-- Th1, Th2 responses would be from samples collected prior to infection?

Dr. Snape: No, they'll be after infection, but they'll be in a range of children that have had placebo and infection, placebo-no infection, and vaccine and infection, and no infection. So we'll get to get an assessment of the variable impact of the vaccine and infection on the CMI profile.

Dr. El Sahly: Okay. So, samples were collected from vaccine-recipient naïve to RSV infection before and didn't have RSV infection in that observation period yet?

Dr. Snape: Yes. We are collecting those samples at the moment. I just want to emphasize that's an active thing that's happening now. We don't have baseline samples, but we are collecting samples from as many children Part A as we can-- Part B as we can to get that phenotype.

Dr. El Sahly: I have a question to Dr. Connelly. So, the children who got nirsevimab, there's 17 maybe of them between those who got and those who didn't and they were given the vaccine. My question is, are these patients in active follow-up, especially with the incoming season to see how clinically and immunologically they will respond to their first season, if you will? Probably first and second with all the permutation, will

they remain in follow-up so we can learn from an immunologic and clinical standpoint the outcome?

Dr. Connelly: So, I will let Moderna clarify, but our understanding is that all these participants will continue to be followed-up for the subsequent RSV seasons.

Dr. El Sahly: And with plans to collect the immunologic samples at the outset of the season and later, just so we learn if their responses are any different.

Dr. Connelly: I believe they will continue to be collected at the study time points. Again, it's our understanding, and I can defer to Moderna for any other plans that they might have.

Dr. El Sahly: I want to go back to slide 19 from your presentation, is it easy to do? If not, I can pull it up on my screen.

Dr. Connelly: I'm not sure if we're able to go back after--

Dr. El Sahly: So, do we have samples from these patients after their vaccination but prior to their infection? These specific patients?

Dr. Connelly: Sorry, to clarify, do you mean the participants that developed severe/hospitalized RSV cases?

Dr. El Sahly: Yes.

Dr. Connelly: Our understanding is that the day 85 collection for those four, for the vaccine recipients, those four, happened after the RSV case occurred.

Dr. El Sahly: Okay. So, that was, I guess, the unlucky component here. Okay.

Do we have any additional questions to either the FDA or Moderna? We can probably go for another five minutes before the lunch break, which is unfortunately cut short already.

I have a question that is more general and it pertains to the duration. If we have additional data-- At the time when we reviewed the maternal immunization data, the studies were ongoing. Now that more time has gone by, do we have additional information pertaining to the duration of efficacy with the second season, etcetera, and how these infants did? It's probably a question that can be answered later if it can be answered. But--

Dr. Connelly: Yeah, thank you for that question. That may be a question better answered by our CDC colleagues, but we can discuss.

Dr. El Sahly: I don't think the CDC would know at the moment because it would be on the clinical trials that preceded the licensing and the recommendation. I understand that it may not be public domain now, but will we see those data soon? And-- Because they might have implications for a few of the percolating questions so far.

Dr. Connelly: We'll take that under advisement. Thank you.

Dr. El Sahly: Okay. Alright. Thank you. Dr. Gans, would be the last question and it has to be brief so we don't make the lunch even shorter.

Dr. Gans: I just have a clarifying question mostly I think for the Moderna, but anyone who wants to answer. What was the stimulation for the T-cell immunity data? I don't know what the antigen stim was.

Dr. Snape: For that question, I'd like to defer to my colleague, Dr. Shaw. Thanks very much.

Dr. Shaw: Hi, Christine Shaw. The stimuli for the CMI analysis were peptides covering the RSV prefusion protein. They were 15 mers overlapping by 11.

Dr. Gans: Thank you.

Dr. El Sahly: Okay, well, thank you all for the presentations, the questions and answers. We have now a break until exactly 12:15 Eastern, for the Open Public Hearing Session. Thank you.

Open Public Hearing

Dr. El Sahly: Welcome back to the Open Public Hearing Session. I invite the Committee members to the raise-your-hand function if you have a clarifying question to the presenters pertaining to the scientific content of their presentation as a clarification point, not necessarily a full-on discussion or give-and-take.

So, this is the Open Public Hearing Session. Welcome to the Open Public Hearing Session. Please note that the Food and Drug Administration and the public believe in the transparent process for information gathering and decision making to ensure such transparency at the Open Public Hearing Session of the Advisory Committee Meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the Open Public Hearing speaker, at the beginning of your oral statement to advise the Committee of any financial interests relevant to this meeting, such as a financial relationship with any company or group that may be affected by the topic of 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'll not preclude you from speaking.

And now I turn the OPH session to Sussan who will be moderating it and taking it for next steps.

Dr. Paydar: Great. Thank you, Dr. El Sahly. Before I begin calling the registered Open Public Hearing (OPH) speakers, I would like to thank all OPH speakers on behalf of the FDA and the Committee for their interest in participating in today's VRBPAC meeting and sharing their views and comments. FDA encourages participation from all public stakeholders in its decision-making processes. Every Advisory Committee Meeting includes an Open Public Hearing Session during which interested persons may present relevant information or views.

I would also like to add the following guidance that the participants during the OPH session are not FDA employees or members of this Advisory Committee. FDA recognizes that the speakers may present a range of viewpoints. The statements made during this Open Public Hearing Session reflect the viewpoints of the individual speakers or their organizations and are not meant to indicate agency agreement with the statements made.

With that guidance, I would like to begin. Let's begin with our first OPH speaker, Mr. Don Ford. Mr. Ford, go ahead.

Dr. Ford: Hi, thank you. I want to say, first off, I have no conflict of interest. Listening to this RSV conversation, obviously this is a very tough nut to crack, there are a couple of things that came across my mind that I wanted to share with the Committee

that might, I don't know if it'll help or not-- But when we talk about animal models, and animal models and human modeling not aligning, well, we use animal models because evolutionarily, we align with these animals at different stages. But there are things that come up where we have gained things that are distinctly human that are post these evolutionary splits. So, a good example of this is the IgG four. In humans, we don't really see that in animal modeling. And when it comes to the mucosal system, we have no problem using mucosal vaccines on animals, but when we go to human trials, there are these huge problems. And I feel like when you're trying to look for a problem like this, it's kind of like looking for a needle in a needle stack. So, identifying where the evolutionary shifts between animals might help you give a focus on where to identify where your animal modeling is coming up short. The other one is that you're talking about a syncytial virus, which is-- Again, we see-- We've learned a lot about this from COVID and we think about syncytial viruses-- Most T-cells don't have a lot of problem actually handling them, but when the T-cell is actually interacting with the virus, it's interacting with the syncytial formation. And that has a completely different process that's often gone unmeasured in a lot of these studies. So, we might see on paper that T-cells should do well against these pathogens, when it actually comes time for the interaction, they can be quite vulnerable to the parasite cells that are inside of these formations. So, I think that this is a measurement that's commonly lost. We see this loss with COVID a lot, and I'm pretty sure that the RSV has a similar mechanism that's also causing this.

Now, my last comment is a little off-topic, but on-topic. I'm very concerned that this is bad for mRNA on the surface with the change in administration coming on. And I think that anything the Committee can do to help bring Novavax pediatric access to market, which is just an expansion of the current available vaccine, because there's a

good chance that RNA is on the chopping block as far as this new administration is concerned, and that can leave us with no childhood COVID vaccine. And there's a good potential-- We might see pressure to not approve new vaccines in the first year or so, and that can put us all in a really tough position. So, anything the Committee can do or the Committee members can do to facilitate that, anything there would be greatly appreciated. I know there's a lot of concern on the ground with people that there's going to be a pediatric COVID vaccine and this would be a solution to that in a bunch of different ways. So, thank you very much. That's all the time I need.

Dr. Paydar: Great. Thank you, Mr. Ford. Our next presenter is Dr. Saman Asad Siddiqui. Dr. Siddiqui, please go ahead.

Dr. Siddiqui: Thank you. Good afternoon. I'm Dr. Saman Asad Siddiqui, a Physician with a Master's Degree in Clinical Investigation from Harvard Medical School. I'm speaking today on behalf of the National Center for Health Research. Our research center does not accept funding from any companies that have a financial interest in our work, so we have no conflicts of interest. Thank you for the opportunity to speak today.

For children under 5 years of age in the US, RSV is associated with an estimated 58,000 to 80,000 hospitalizations and 100 to 300 deaths annually. The recent Phase I study of mRNA RSV vaccines conducted by Moderna in infants aged 5 to 7 months, raised significant safety concerns. Among the 40 infants who received a 15 microgram dose of the RSV vaccine, 16 developed symptomatic RSV disease, and of these 5 progressed to severe or very severe lower respiratory tract infections. In contrast, among the 20 placebo recipients, 12 developed symptomatic RSV disease, but only 1 experienced severe or very severe lower respiratory tract infections. This means that overall 12.5% of the vaccine recipients experienced severe or very severe RSV lower

respiratory tract infections compared to the 5% of the placebo group. Of the 6 severe cases identified in this study, 5 required hospitalizations and 1 infant required mechanical ventilation and the medium time for resolution of these severe cases was 19.5 days. While the small sample size limits the certainty of these findings, the higher rates of severe illness in vaccine recipients compared to placebo raises serious concerns about the vaccine safety for infants in this age group. These findings led to a study pause and discontinuation of the RSV program for seronegative children under 2 years old, which we can all agree indicates the challenges in developing safe ineffective RSV vaccines for young children. While established safeguards exist for RSV vaccine development, this study suggests they may not be sufficient to prevent all potential safety issues, particularly in RSV-naïve infants.

So, to enhance the safety of RSV vaccine development for infants and toddlers, we urge that several actionable steps should be prioritized. First, we agree with the FDA scientists that there must be a reassessment of clinical trial designs. This should include implementing stringent safety monitoring protocols with continuous real-time data analysis, considering lower initial vaccine doses for younger age groups, and increasing the frequency of interim analysis with predefined thresholds for study pauses. Secondly, enhanced immune profiling is essential as outlined in the WHO guidelines. This involves conducting comprehensive analysis of T-cell responses, focusing on neutralizing antibody functionality and evaluating mucosal immunity alongside systemic responses. In addition, we recommend accelerated biomarker research focusing on large scale genomic and proteomic studies of infants with severe RSV disease post vaccination and developing predictive in-vitro assays to assess vaccine-associated ERD risk prior to human trials, ensuring safe and more effective vaccines.

Additionally, animal models need to be approved to better replicate-- I'm sorry. Models need to be improved to better replicate human RSV disease and vaccine-associated ERD as suggested by the WHO guidelines by conducting comparative studies across multiple models.

Finally, we would like to highlight the need for a global RSV Vaccine Safety Consortium to facilitate collaboration among researchers, clinicians, and regulators. This will help to ensure rapid data sharing and standardized safety assessments across trials while developing harmonized protocols for vaccine associated ERD risk assessment and management. By prioritizing these steps, we can significantly improve the safety profile of RSV vaccines for the pediatric populations.

In conclusion, while progress has been made in RSV vaccine development, the recent study underscores the need for continued vigilance in our approach. We must balance the need for an effective RSV vaccine for children with the paramount importance of safety for children participating in these clinical trials prior to approving a vaccine. By addressing these challenges head on, we can work towards a safe and effective RSV vaccine that could significantly reduce the global burden of this disease in our most vulnerable population. Thank you.

Dr. Paydar: Great. Thank you so very much. Our next presenters are Dr. Biao He, Founder and CEO, and Dr. Henry Radziewicz, Chief Medical Officer, Blue Lake Biotechnology. Dr. He, please go ahead.

Dr. He: Okay. Thank you. Can I have a first slide, please? My name is Biao He, Founder and the CEO of Blue Lake Biotechnology, a clinical stage intranasal vaccine company. I'm also the inventor of the intranasal vaccine platform based on parainfluenza virus 5 (PIV5). We're based in Athens, Georgia, and in San Jose,

California. I want to thank the FDA for giving us this opportunity to present our work and perspective on this very important topic. Next slide.

We want to cover four areas today. We want to introduce our intranasal PIV5 vaccine platform; and present an overview of the RSV vaccine using intranasal live replicating viral platforms expressing RSV wild type F protein, which have never been associated with vaccine associated enhanced respiratory disease, VAERD; and present data on BLB201, an intranasal live PIV5 based RSV vaccine expressing wild type RSV F. Finally, we will propose a path forward for BLB201. Next slide.

As presented today by Dr. Dawood, RSV causes significant mobility and mortality in infants and young children. Our goal is to develop a safe and efficacious RSV vaccine for them. Next slide. Please, play the video.

Our vaccine is based on the life attenuated PIV5 component of Kennel cough vaccine. This live-attenuated virus has been intranasally delivered to dogs for years. Dogs can shed this virus for up to five days after they're intranasally immunized. Considering about 40% Americans have pet dogs, many people including infants, young children, elderly and immunocompromised people have already been safely exposed to this live-attenuated PIV5 for decades. Importantly, our live-attenuated PIV5 vector replicates in the host and is different from other viral vectors that are replication-defective or single-cycle. We have used this live-attenuated PIV5 platform to express various antigens. At present, we have two clinical programs: PIV5 based intranasal COVID vaccine, and PIV5 based, again, intranasal RSV vaccine. Next slide.

Safety is our top consideration for vaccine development. Safety considerations for infant RSV vaccines include not only reactogenicity, but also importantly, VAERD. Since natural RSV infection does not cause VAERD, many became RSV infections

such as intranasal delivery, use of live-replicating virus, and use of a wild type antigen has been employed. As presented early today by Dr. Piedra, and in this paper by Dr. Ruth Karron, intranasal live-replicating virus expressing wild type RSV F does not cause VAERD in the case of live-attenuated RSV vaccine. Next slide.

Similarly, life replicating bovine human parainfluenza virus 3, Camero virus, delivered intranasally that expressing wild type RSV F MEDI-534 was tested in over 200 infants and no VAERD was observed. Thus, we believe intranasally delivered live-replicating virus that expressed wild type RSV F has never been associated with VAERD. Next slide.

As mentioned earlier, we have two clinical programs. Our intranasal COVID vaccine expresses the S protein of SARS-CoV-2 and we have enrolled over 300 people in Phase I and Phase II A. Our Phase II B trial is targeted to enroll over 10,000 people. Half of that will receive our intranasal vaccine. Our PIV5 vector intranasal RSV vaccine expressing wild type RSV F protein has enrolled over 90 people ranging from 8 months to 75 years old. Both intranasal vaccines have been safe and well-tolerated in our current clinical trials. Next slide.

As described early this morning, a dysfunctional immune response to vaccine, especially a Th2-biased immune response after immunization may be a signal for VAERD. In our Phase I study of our COVID vaccine, we observed a balanced immune response including moderate serum antibody response and cell mediate immune responses including CD8 positive T-cell response. We did not observe Th2-biased immune responses in SARS-CoV-2 naïve or experienced participants as indicated by the absence of AEs specific IL-13 expressing T-cells. IL-13 is a Th2 cytokine.

In Phase II, a study of our COVID vaccine 78% protection against the symptomatic COVID infection was observed. In comparison, existing COVID vaccines have 52% vaccine efficacy at one month after immunization. Thus PIV5-based intranasal COVID vaccine is a safe, well tolerated and indicative of efficacy, and it does not induce human immune responses that are associated with VAERD. Next slide.

We have developed BLB201, the PIV5-based RSV intranasal vaccine expressing wild-type RSV F. We [Indiscernible - 1:30:36] live-attenuated vaccine as well as the MEDI-534. We use wild-type RSV F, full-length RSV F, with no mutation for mRNA vaccine. As described today, they used the ones with mutation that will introduce- To keep the F protein to mimic the prefusion confirmation of the F protein. Well, this was believed by some to reduce the likelihood of VAERD. The data presented today showed this was not necessarily correct. We also learned from today's presentation that the very high neutralizing antibody response is not the key to preventing VAERD asymptomatic infection in infants. Thus, the BLB201 is safe and efficacious in preventing RSV infection in mice, cotton rats and the non-human primates.

The cotton rat model is considered the gold standard to evaluate VAERD risk and BLB201 at different dose levels and did not cause VAERD in this model. Next slide please.

Besides testing in cotton rats, we have also exempted potential VAERD signals in non-human primates. As presented early the Th2-biased immune responses and absence of CDA positive T-cell responses or thought to be associated with the VAERD immunization of non-human primate with all vaccine did not lead to a Th2-biased immune response as indicate that lack of IL-4, 5 and 13 expression in serum, but it did

lead to a CD8+ T-cell response further indicating that the BLB201 does not induce immune responses that are associated with VAERD. And following the discussion this morning from Dr. Piedra's presentation on the lack of VAERD with Merck formally inactivate vaccine which contained a mixture of both formerly inactive RSV and formally inactive PIV. It is tempting to suggest that a live replicating intranasal vector vaccine such as PIV5, is the ideal candidate because it contains both RC antigen and a live replicating viral vector. Next slide please.

So, in our PhaseI1 clinical study BLB201 induced moderate antibody responses and cell mediate immune responses including CD8+ T-cell response. No Th2-biased response was detected consistent with PIV5 as a life replicating and attenuated virus limited replication of BLB201 was detected in humans. BLB201 was safe, well tolerated and induced a balanced immune response in 33 to 75-year-olds. Importantly, the mechanism of action of a vaccine is not to induce extremely high antibody responses, but instead to efficiently present RSV antigen to the mucosal immune system, targeting mucosal rather than the serum antibody responses further reduces the likelihood of VAERD. Now, Dr. Radziewicz, our CMO, will describe our Phase I and IIa infant RSV trial. Next.

Dr. Radziewicz: Thanks, Dr. He. The primary goal of our study is to evaluate the safety of our vaccine in healthy 6 months to 5-year-old infants and children. We are also evaluating immune responses in serum and nasal secretions. To ensure the safety of participants in our study, we have instituted measures to the design including the use of sentinel cohorts, use of low dose vaccine prior to high dose, enrollment of older children prior to younger age groups. Amongst the other measures shown in the slide. We closely track all medically attended adverse events, any serious adverse event, all

RSV infections, and all lower respiratory tract infections including croup, bronchiolitis and pneumonia, whether related to RSV or other pathogens. Next slide.

The table at the top shows our enrollments to date. As I noted on the previous slide, we enrolled older children and used lower dose vaccinations first, as noted in groups 1, 2, and 3 for safety. We have a completed enrollment of these three groups. Including groups 4 and 6, ages six to 24 months, 25 of 48 plan participants have already been enrolled and received a single dose of high dose vaccine. 23 RSV seronegative participants less than two years of age are enrolled in the study. 11 had their first RSV exposure last season and 12 are being exposed for the first time to the current RSV season. By next March, all 63 infants and young children enrolled in our study will have gone through at least one RSV season.

BLB201 pediatric vaccine has been well tolerated and safe in infants and young children. No vaccine SAE nor any vaccine related medically attended adverse event has been reported. A total of eight symptomatic cases of RSV have been diagnosed. All cases of symptomatic RSV have been graded as mild or moderate with no severe case. No participant has required hospitalization for RSV infection, nor has there been any hospitalization related to any respiratory tract infection to date in our study. We previously unblinded the immune data for groups 1 and 2 seropositive participants. We found serum neutralizing IgG/IgA and nasal IgA antibody response ranging from 60 to 80%. In contrast to mRNA-1345 whose post immunization neutralizing antibody and binding antibody showed 149-fold and 338-fold increases over baseline in Part A of its trial, our vaccine generated modest 8.4 fold neutralizing antibody and 2.5 fold IgG binding antibody after immunization in our seropositive children. We also detected a 2.3-fold rise in nasal IgA mucosal antibody response.

The fact that BLB201 replicates even in seropositives and induces an immune response suggests that it would present sufficient antigen to be highly effective in seronegatives. Based on the clinical data so far, there is a statistically significant reduction in symptomatic RSV cases among our BLB201 vaccinated infants and children of at least 80% over placebo controls. This strongly suggests that the immune mechanisms after BLB201 vaccination are very different from that of formalin-inactivated vaccines and mRNA vaccines indicating that the BLB201 vaccine is unlikely to lead to similar immunologic VAERD. Based on our preliminary result of at least 80% protection, we do not feel that further demonstration of clinical benefit in a seropositive infants and children would bring additional value to assessment of the risk of VAERD. Also, this group is not the primary target population for an effective pediatric vaccine. Next slide.

We believe that it is safe for our BLB clinical trial to proceed and to include additional seronegative participants. We have instituted measures to help ensure safety that are noted further in this slide. We and an independent Data Safety Monitoring Board review any participant with RSV infection in real time and our study uses safety pausing rules that includes severe RSV infection in any single participant. Next slide.

We strongly believe that our live-attenuated replicating virus vectored intranasal RSV vaccine expressing wild-type F protein is not a risk for VAERD. Such vaccines like BLB201 and MEDI-534 have never been associated with VAERD. BLB201 vaccination does not induce a Th2-biased response, neither in animals nor humans and we do not believe that additional animal studies or studies in seropositive infants and children would be helpful. We have enrolled 63 children with no indication of VAERD to date. Most encouragingly, there is an early indication of vaccine protection of at least 80% in our study. Further testing of BLB201 in seronegative children is essential to

confirm the safety and efficacy of this vaccine. While there has been progress in the field of RSV prevention, many children who experience severe infection are still not protected. Developing a safe and effective vaccine remains an urgent public health need. Blue Lake is ready to work with the FDA and VRBPAC to permit continued development of our highly promising vaccine candidate. Next slide.

Thank you very much. Additional information can be found on this website.

Dr. Paydar: Great. Thank you so very much for your presentation. I don't-- I see a hand. Dr. El Sahly has a question.

Dr. El Sahly: I have a brief question to Dr. He. Dr. He, in the 11 seronegatives-- Yes.

Dr. Paydar: AV Team, if you could go back to the slide.

Dr. El Sahly: I don't know, Susan. Your volume went down. We can't hear you.

Dr. Paydar: I would like the slides to go back.

Dr. El Sahly: Okay, so were there immunologic assays performed on the 10 or 11 seronegative children who got your vaccine, in terms of TH1, TH2 biased. I know you showed us data from different other studies.

Dr. He:We have gotten the data from the group 1, 2, 3 and 4 in terms of serum and antibody data, et cetera. We also are working on, and we do collect some PBMC, to look at the T-cell data as well. However, we have not unblind the group 3 and 4, so we don't really know what the results will be, but we have a separate committee looking at the cases then of eight symptomatic cases. So, that's separate from looking at the immunogenicity. The only immunogenicity data we have unblinded was from group 1

and group 2. Those are RSV positive kids who have gotten low and high doses and that's what we have. For the rest, we have data but it's still blinded.

Dr. El Sahly: Okay, great. Thank you.

Dr. He: Thank you.

Dr. Paydar: Thank you so much everyone. El Sahly, can you hear me?

Dr. El Sahly: Susan, your audio is very poor. I don't know. Am I the only one who can't hear Susan?

Dr. Long: We can't hear it either.

Dr. Paydar: Next presenter. Please go ahead with Dr. Sridhar.

Dr. Sridhar: Thank you. I hope you can hear me.

Dr. El Sahly: Yeah, we can hear you very well.

Dr. Srihar: Thank you. So on behalf of Sanofi, I'd like to thank the committee for giving us the opportunity to present an update on Sanofi's pediatric RSV vaccine development today during today's VRBPAC meeting. My name is Saranya Sridhar. I'm a full-time employee of Sanofi. I've been in the Clinical Department of the company for eight years and I'm the head of Clinical Development for Vaccines. Next slide, please.

There is an unmet need for children in their second RSV season, which has significant health and economic impact to children, their families and health services. This slide provides some of the data that underlines the scale of this public health challenge. Global estimates of RSV burden in toddlers stands at 33 million cases every year. In the US alone, this represents approximately 2.1 million children requiring

medical attention each year. 60% of children have multiple RSV infections before they reach 3 years of age with some of the consequences of infection, including pneumonia and otitis media. This health burden is mainly carried by outpatient health services, but one third of all RSV hospitalizations in children under 5 years of age is because of RSV infection in toddlers. These numbers taken together signifies substantial financial and emotional burden on families. Next slide please.

Beyond the numbers, the clinical spectrum of disease caused by RSV in toddlers as illustrated in this slide is notable. Toddlers can suffer from upper and low respiratory tract infection like infants, but also respiratory complications and exacerbations of wheezing, like older adults. As you are well aware, there have been significant advances over the last few years in RSV preventative strategies. In infants, we now have long-acting monoclonal antibodies as well as maternal immunization while three vaccines have been approved for older adults. Thus, it is remarkable that despite the burden and wide clinical spectrum of disease and toddlers, we do not yet have a preventative strategy for this population. Next slide please.

As we heard earlier today, vaccine development efforts for the pediatric population were initiated as early as the 1960s. However, these efforts were set back by the observation of enhanced respiratory disease with a formalin-inactivated RSV vaccine. VAERD was characterized by three observations. First, the numerical imbalance of severe lower respiratory tract disease following vaccination was observed in children naïve to RSV prior to vaccination. Second, these cases were observed in the first year of follow-up after vaccination. And third, the respiratory pathology showed immune complex deposition and eosinophilia in the lung suggesting a Th2-biased response. It is noteworthy that this phenomenon has not been observed in the context of natural infection and subsequent vaccine development has focused on mimicking

natural infection. Live-attenuated vaccines delivered intranasally have been developed with rationally designed genetic modifications to remain immunogenic while ensuring an optimal safety profile and to minimize the risk of enhanced respiratory disease. Sanofi has been in collaboration with the United States National Institute of Health to develop the live-attenuated vaccine platform. Next slide, please.

The US NIH has pioneered the development of a live-attenuated vaccine platform for RSV. 16 different live-attenuated vaccines have been evaluated in a careful stepwise approach to identify safe and immunogenic candidates. The first trial started in adults with careful dose escalation before moving to Phase I studies in RSV experience toddlers. Only after demonstrating safety and suitable attenuation in these populations were studies initiated in RSV-naïve toddlers. Through this careful stepwise approach over the last 30 years, NIH in collaboration with Sanofi identified the SP0125 vaccine candidate as our lead candidate with an optimal combination of safety and immunogenicity. The SP0125 vaccine was evaluated in a Phase I/II dose escalation study in children before entering Phase III evaluation earlier this year. Let me share some of the details of the design of the SP0125 candidate. Next slide please.

The SP0125 vaccine contains three key genetic modifications to attenuate the vaccine and to make sure that these attenuations are stable. First, a deletion in the NS2 gene, which attenuates the virus and removes the risk of NS2 mediated airway obstruction. Second is a deletion in the polymerase gene, which confers temperature sensitivity and restricts replication at a temperature of 38 to 39°C. And third, this temperature sensitive deletion is stabilized by a missense mutation in the adjacent amino acid of the polymerase gene. These rationally designed modifications combined to ensure that the vaccine would restrict replication in the upper respiratory tract, and

we have generated data in over 4,000 toddlers that the infectivity, which mimics natural infection, is not compromised with these modifications. Next slide please.

NIH and Sanofi have generated data on the live-attenuated vaccine platform in approximately 4,000 children. The NIH have run trials with 16 live attenuated vaccine candidates in approximately 800 participants, and over a surveillance one RSV season there has been no evidence of vaccine associated enhanced respiratory disease observed in these trials. Our SP0125 vaccine candidate has been administered intranasally to over 3000 children. No safety concerns have been observed to date by us and our independent Data Monitoring Committee. Next slide please.

These live-attenuated vaccines have not only shown to be safe as a platform but have also shown protective benefits. This is data published by Professor Ruth Karron and colleagues, which compiled the efficacy observed across different clinical trials in children of eight live-attenuated RSV vaccine candidates. In this forest plot, the black lines show the average efficacy of eight different vaccine candidates against medically attended acute respiratory illness caused by RSV. The blue lines represent efficacy observed with a subset of five lead candidates out of these eight. The top two lines present data from all vaccinated children, while the bottom two lines are a subgroup analysis of children who were determined to have a neutralizing antibody response post vaccination.

This forest plot with vaccine efficacy plot on the X axis shows that if you're to the right of zero, there is protection and benefit while to the left would suggest increased risk. As you can see from the graph, a protective effect was observed for these vaccine candidates and for the five lead candidates, the average vaccine efficacy was 67%. The SP0125 vaccine that we are now evaluating in a Phase III trial was among these five

candidates. When the analysis was restricted to neutralizing antibody responders, the blue lines on this graph, we observed similar vaccine efficacy suggesting a link between having an immune response to the vaccine and protection against disease. These results provide evidence of the protective potential and benefit of these live-attenuated vaccines against RSV without any evidence of an increased risk. Along with the safety data from careful stepwise de-escalation, it formed the basis for us to select the SP0125 vaccine to advance to clinical development. Next slide please.

Our SP0125 vaccine candidate was evaluated in a Phase I/II study in children six to 18 months of age. A low dose and a high dose formulation were evaluated and compared to a placebo. The way the data presented here is a classical reverse cumulative curve where you have the neutralizing antibody titers and the X axis, and the percentage of volunteers on the Y axis. This is data from children who were RSV-naïve prior to vaccination. What is key here is that the two formulations induced a nice shift of the curve to the right, reflecting a substantial increase of neutralizing antibody in most volunteers and showed little difference between the load and the high dose formulation in the study. Along with the favorable safety profile, these immune data that were consistent with prior studies provided the evidence to advance our candidate to Phase III clinical development. Next slide please.

Our Phase III efficacy trial initiated in February of 2024 earlier this year is placebo controlled and designed to demonstrate the safety and efficacy of this vaccine against upper and lower respiratory tract RSV disease, including severe disease and hospitalization. The presence of efficacy against severe lower respiratory tract disease will also demonstrate the absence of vaccine associated enhanced respiratory disease.

I'd like to draw your attention to some key elements of the study design. First, the population of toddlers 6 to 22 months of age eligible to participate in the study includes those with previous receipt of nirsevimab in their first year of life. A subset analysis will generate safety and efficacy data in nirsevimab experienced children, which of course is relevant to the discussion today, but will be very relevant at the time of deployment. Second, we are targeting 50 to 70% of our participants to be RSV-naïve at the time of vaccination. This will allow us to generate efficacy and safety data in those who are at highest risk of vaccine associated enhanced respiratory disease. And third, the children are followed for RSV illness over two seasons generating long-term efficacy and safety data. Next slide please.

I'd like to share some aspects of our program, particularly with relevance to safety surveillance. Considering the observation of vaccine associated enhanced disease, we have initiated disease surveillance from our first Phase I/II trial, which has now continued into our Phase III program. This includes both active and passive surveillance for the detection of any RSV in the upper and lower respiratory tract. And in addition to our own safety monitoring team as a sponsor, the program is monitored by an independent Data Monitoring Committee. To date across our program, approximately 900 children have received the vaccine and have completed follow-up over at least one RSV season. No evidence of vaccines associated with enhanced respiratory disease has been observed in these children. Now that we've shared the data we have collected to date on this vaccine, how do we see it working with other prevention strategies for children? Next slide please.

The SP0125 vaccine targets toddlers to protect them against RSV during their second season and aims to work with nirsevimab, which protects infants in their first year of life. As mentioned before in our program, we will be generating data on the

clinical efficacy and safety of the SP0125 vaccine in children who have received nirsevimab. And here is how we see it working in practice. Let's take the example of a baby born in the US in June. They will receive nirsevimab at three to four months to protect them for the whole first season. And at the end of the first RSV season, when they turn nine to 10 months, they will be offered two doses of the RSV toddler vaccine and that is expected to provide protection for the second RSV season. Next slide please.

In summary, the development of RSV pediatric vaccines requires careful stepwise age de-escalation studies to demonstrate safety before initiating a Phase III program. Over the last 30 years, NIH in collaboration with Sanofi have taken this approach to demonstrate the safety and potential benefit of live-attenuated vaccines. These decades of research led to the generation of data to initiate Sanofi's SP0125 vaccines Phase III efficacy trial. The design of the Phase III study allows us to provide a unique set of data to demonstrate efficacy against severe disease and thereby the absence of enhanced disease over the course of two RSV seasons. To date, no safety concerns have been identified in over 3000 children who've received the vaccine and in 900 children followed over one season. We are confident that the development of the SP0125 vaccine addresses an important medical need for infants and toddlers, and in combination with currently available preventive strategies for infants will fill the gap to provide complete RSV protection during childhood. Next slide please.

Thank you for your attention. And I'd like to thank the Committee again for the opportunity to present at this meeting.

Dr. Paydar: Great, thank you, Dr. Sridhar. Can everybody hear me?

Dr. El Sahly: Yes, we can.

Dr. Paydar: Finally. That's a relief when the DFO phone works. Okay. All right. Well, thanks everyone for your patience. I don't see any questions from the Committee for any of the OPH presenters.

Dr. El Sahly: I do.

Dr. Paydar: You do. Oh, I just saw your hand. Okay, go ahead.

Dr. El Sahly: Just a very brief question to Sanofi colleagues. A clarifying question. Is the Phase III clinical trial now fully enrolled per the sample size calculation at the outset?

Dr. Sridhar: It is not yet completely enrolled.

Dr. El Sahly: Oh, okay. Thank you so much.

Dr. Paydar: Great. And I see another question from Dr. Perlman.

Dr. Perlman: Yeah, I just had a question about the live-attenuated vaccine. What kind of studies have been done to prevent or to examine the possibility of reversion and recombination so that one gets back [Indiscernible - 1:59:38] virus?

Dr. Sridhar: Thank you, Dr. Perlman. So, we have done initial studies where we've given the children a vaccine and in fact did pairs in a daycare setting to look at transmission in a daycare setting as well. And in those studies we haven't found any transmission, but we've also looked at reversion and we haven't seen any reversion in the vaccine virus.

Dr. Perlman: Have you monitored for recombination as well?

Dr. Sridhar: I believe so. I can check and let you know.

Dr. Perlman: Okay.

Dr. Paydar: Great. Any other questions from the Committee? If not, thank you everyone once again for participating in today's Advisory Committee and for sharing your views and comments. This concludes the Open Public Hearing Session for Topic I and now I hand over the meeting back to Dr. El Sahly. Dr. El Sahly, you could please start the next session.

Committee Discussion of Considerations for Respiratory Syncytial Virus [RSV] Vaccine Safety in Pediatric Populations

Dr. El Sahly: Yes. Thank you, Sussan for moderating the OPH. Now is the time when we will be discussing as a Committee and asking additional questions pertaining to the two topics of discussion.

The first topic is the more involved one and projecting that it'll occupy the majority of the time. We're allocating an hour and 20 minutes for it, but who knows, it may be a little shorter, a little longer. Sussan, do you mind pulling the first question or both questions on the slide so we can-- Yes. Thank you. So, that's Topic I. I'll read it out loud and in the meantime, please prepare your discussion points and questions and use the raise hand functions so I can call on your name.

Please discuss whether the currently available evidence indicates a potential safety concern more broadly applicable to the evaluation of RSV vaccine candidates in infants and toddlers. Please discuss the applicability to: different vaccine technologies (e.g., live-attenuated RSV, viral-vectored, mRNA and subunit.) And b) different antigenic confirmations (e.g., stabilized preF or other RSV protein prototypes.)

The second part is: Based on the currently available evidence, please discuss current nonclinical and clinical safeguards, and recommend whether any additional nonclinical and clinical information should be considered and/or precautions taken when evaluating RSV vaccine candidates in infants and toddlers. Dr. Gans.

Dr. Gans: Thank you very much. I think this is a very important conversation and I really appreciated the additional information that was provided to us through the open remarks. In terms of what I think really needs to happen is that given that much of the data that we have from previous vaccine attempts is from a time when we didn't actually have the capability to do immunology the way that we can do it now, I think we actually need to go back to what natural disease actually provides in terms of immunity and understand that we still have a lot of circulating RSV, we still have plenty of children who can be categorized as mild or severe, and once we have that, then we can really understand these platforms better. And we know that people who gain their immunity in that way, as their primary immune response, which is the goal obviously for vaccination, would be then protected against more severe outcomes.

And I think that is the process that would be very nice with current modern technologic techniques. I loved the data that individuals presented on the live-attenuated RSV models that they're producing, which did dig into that a little bit more. However, it's not showing again the immune responses as it compares to natural disease, but obviously is showing us some CD4, CD8 data and immune profiles that come from that as well as neutralizing antibodies. I think what we've learned from the presentations today is that you do need a balanced response. So, I think not trying to have a Th2 response isn't the whole picture. Not only trying to have neutralizing antibodies to one form of the S-protein is the picture. So that's why I think going back to having a really clear understanding of what a good regulated immune response means typically it

actually provides many of the different parts of your immune system so that you get a good bump, but then you actually have that turned off. I think it's really important to understand all of that.

I think that the profile that we did see just answered the question a little bit. It was concerning for the messenger RNA, and it appears that other individuals who are looking at different platforms actually haven't shown that. I don't know that the issue that we're seeing with that is actually more global and I think each of these need to be taken separately and understand the immunology separately. The other piece of it that I think really needs to be investigated further is the-- Which we heard a lot about the monoclonal antibody and then the immunization. We need to understand maternal immunization followed by infant or toddler immune responses. I think it's really encouraging that we have the ability to passively protect our very young infants and then immunize them when they're confronted potentially with a second season. So, those are some of my thoughts on the question.

Dr. El Sahly: Thank you, Dr. Gans. Dr. Monto.

Dr. Monto: I think we are confronted by a very complicated situation. We know that passive acquisition of an antibody is protective, highly protective, and does not produce severe disease in any way. We now have a platform which should be only inducing antibody formation, which I think it's pretty much the right antibody, the fusion antibody. I think it's very clear that there is a safety signal and the trials cannot continue, at least in the youngest age group. I don't see this. Based on our understanding and our ability to develop any kind of new markers for severity that we can stop or should stop development of potential vaccines using other platforms because we really don't understand the relationship of the platform to the severity nor different

antigenic confirmations. Certainly, the stabilized prefusion would be the one to follow. Therefore, just cutting to the discussion topic, I think this needs to be done on a vaccine platform by vaccine platform basis and to continue with the very careful age de-escalation and pre-infection, previous infection approach, but to do it with great caution and to make sure that if there is a signal it is caught and appropriately handled. Thank you.

Dr. El Sahly: Thank you, Dr. Monto. Dr. Kotloff.

Dr. Kotloff: Yes. I'll repeat a little bit of what I said before because I think it's so interesting that if you have an mRNA vaccine that makes an antibody to the prefusion F vaccine, you have protection with the monoclonal antibody but not with the antibody to that single protein. So, that to me is very confusing and I feel like it's a message. It's just really a scary slippery slope that we're on because these reactions can be so severe. I actually also wonder if the reactions that we're seeing are in any way related to the kids that we see that come into the ICU that are also off the standard curve, previously healthy kids who get such severe RSV. I think studying those a little bit more would be interesting. But I think for me, the safest path is knowing that maternal antibody and monoclonal antibody are protective. The approach that we heard of giving that to protect kids in the first year, trying to get cheaper antibodies made and then use vaccination for kids after the first year of life to me seems the safest way forward to avoid the safety signals that we don't really understand. Thanks.

Dr. El Sahly: Thank you, Karen. And as I'm reading the discussion topic and the discussions this morning, especially with the CDC colleagues and the other presenters, it is apparent that we are in an evolution time and we do not know where the new baseline is going to be. The data from the clinical trials on the maternal vaccine should

have data on two seasons so far, probably they are being cleaned up to be presented, et cetera. The nirsevimab had a shortage in the first season. This season may be more reflective of the status quo again, and at IDWeek this year we heard of even more products paralleling the nirsevimab approach that are showing data. So, we are in the coming couple of years in a flux situation to understand where the new baseline is going to be in terms of those most in need of a vaccine.

The economic considerations always come up, the cost of healthcare utilization, absenteeism from work for the parents, et cetera. But to me, well what weighs in heavier is really the morbidity and the mortality and understanding where the morbidity and mortality is going to land after all these new measures are in a status quo mode is critical to understanding the risk benefit of how to construct the clinical trial and who should be tested, and what can and cannot be allowed or tolerated I should say. Having said that and hearing the presentation this morning, the manufacturer did what we expected them to do and the data were very reassuring in terms of binding to neutralizing ratio in terms of safety in older age cohorts in terms of Th1, Th2 biases in animal models and in seropositive children who did get the vaccine. It seems that the moment you get into the unexposed infants, the predictive value of all these steps goes down.

So, it remains that these infants, these seronegative infants have no animal model that predicts their response to a degree, nor do their older seropositive counterparts predict their response either. That is a conundrum. It is possible that in six months from now, many of the data that we heard are being generated will give us new information and then potentially new paths forward or additional safeguards can be put before reaching those vulnerable seronegatives. But at the moment it's hard to predict. The preF versus postF situation is-- We thought that we would want mostly the preF,

but this because of its neutralizing component. But this data shows that probably this does not apply to the seronegatives infants, and there is more to the story there that we don't understand.

When it comes to platform, the data and the summary presented from Dr. Karen's paper and the other manufacturers, et cetera, with a live replicating extenuated RSV, I think there has been enough subjects, enough RSV seasons to potentially give a reassurance there that this particular sequential cautious approach may be acceptable. I don't think I've seen data that give reassurance to other platforms or reassurance for a particular path to study the other platforms. So, this is where I think we stand and I really look forward to some of the outstanding data from the immunology of these trials and infants and knowing what happened in the additional follow ups of the other trials. Dr. Ruckwardt.

Dr. Ruckwardt: Thank you. You can hear me?

Dr. El Sahly: Yes, we can.

Dr. Ruckwardt: I want to also thank everyone for really great presentations today. I think this is a really important and interesting topic. I think when thinking about this first question, the A is really where the emphasis is for me. I think with regard to B, we've learned so much over the last 10 years about the importance of preF and optimizing the antigen and what it takes to elicit great neutralizing antibodies. And we know that if you have great preF antibodies, whether it's monoclonal or polyclonal, you can get protection. The problem here becomes more complicated because now we find that even though we couldn't predict in animal models, we can elicit those great neutralizing antibodies. And still in that context, these RSV-naïve infants are really

uniquely susceptible to disease, maybe because of some kind of imprinting of cell media immunity, whether it's toward Th2 or IgG4 or a profile like that.

I think one of the things that strikes me is there's still so much more to know, and I think there's a lot of unique opportunities here, particularly even in the group of 8 months to 24 months where we did see a difference in the response to immunization and haven't really explored how that kind of imprinting is affecting the resultant response post-infection in those infants. Even though they didn't end up with clinical severity, they could end up with a difference in immunity that really should be explored. So, I think there's a ton here to explore both in that very youngest cohort, but also we could learn a lot even in the group where we didn't see disease, but also we saw no protection despite having great neutralizing antibody responses. I think-- I hope we can all take advantage of this opportunity. I think I'm echoing the sentiment of others that I think this is very going to be platform dependent. I'm not worried about the live-attenuated because of the long history of safety there. And I think where we can predict that there would be problems using animal models like for subunit, that's a clear indication we should avoid those types of things. Right? But there's still some question about what may happen with other viral vectors or even other mRNAs if you could in some ways skew the response, skew the way you're directing the cell mediated immune response. Thank you.

Dr. El Sahly: Thank you. Yeah, I guess the-- In the animal model and in the older children, the response seemed to have been Th1 with little to no Th2. It's only when it went into seronegatives did the response to the mRNA change or at least give a hint at the change with the dearth of analysis that was done so far. So, I don't know. But I do want to highlight what Dr. Ruckwardt said. And I also didn't mention it. There was not even a signal at efficacy in the seropositives. The incidence was very comparable and

understanding that this is a very small sample size, but with that there was no signal of efficacy to speak of. Next is Dr. Piedra.

Dr. Piedra: Thank you. I would like to kind of just make a comment, and that is that I think RSV vaccines are going to be extremely beneficial once we understand well the issue of safety and risk in younger infants. Right now, we have nirsevimab, which is an outstanding monoclonal antibody that is providing high levels of protection against severe disease. But I want to call your attention that it's a monoclonal antibody and if history has taught us well, when you use a monoclonal antibody in such a universal format, you need to expect that mutations will occur and that you may develop either a resistant virus or a community resistant emergent virus that will be resistant to that monoclonal antibody. And so, to rely on the monoclonal antibody to provide protection during the first year of life would raise that caveat that infants are an excellent vector in a way that if mutations are to arise, it would be an infant or immunocompromised host. Because infants have long-- First, they don't have a good immune response, but two viruses replicate for many rounds of replication. And that is the way that in an invitro system, you can generate resistance rather readily to monoclonal antibodies. And so I want to bring that to the attention because I don't think we can only rely on monoclonal antibodies forever and being able to protect infants during the first year of life and that we need to think downstream that vaccines will provide broader levels of responses that may be applicable and hopefully safe in the young population. The other comment that I would like to make is: I think y'all all understand that platform matters and not only does the platform matters, but probably the route that the platform is used probably matters as well in the sense of a mucosal application versus systemic application. And those will probably elicit quite different responses. Thank you.

Dr. El Sahly: Thank you, Tony. Dr. Perlman. Dr. Perlman, you have your hand.

Dr. Perlman: Yes. Sorry. I did. So, sorry. Yeah, so I was just going to agree with most of what was said, but I just wanted to emphasize a couple of points. One is that what we may be seeing may be something that's very difficult to actually investigate because it may be actually occurring in the infant's lungs. So, there may be interactions there between some of the T-cells and other factors that we don't completely understand, and that'll be very hard to investigate, especially since we don't have an animal model that duplicates that because that's exactly when you'd need an animal model. I think that while understanding what happens in the natural infection is really critical also, we may just have to go ahead and answer the first question by saying, yes, continued studies should be done because the results may be quite different from what we saw at the mRNA vaccine.

The mRNA response to the vaccine really is puzzling to me because it seems like we got the right response. I mean, there are subtle differences from what we think is perfect, but it looked pretty good. So, I wonder if we're coming to the possibility that was introduced in Dr. Piedra's talk that we actually had an excessive immune response and that the mRNA vaccine may have worked too well or maybe just modestly imbalanced. So all that would be different potentially with different vaccine platforms. So, I think-- I really support going ahead with future studies and future vaccine analysis because not only don't we have a good handle on what's going on, but we may not really get, even in the next year, really great results from analysis of blood samples that'll really help us.

Dr. El Sahly: Okay, thank you. I don't think though that what's on the table and the FDA can correct me that no research on new vaccines should happen. It's basically, it's more, I guess, nuanced in that given the identified safety concern, how does it apply to

other technologies and confirmations, et cetera, and what additional studies would we want, et cetera.

Dr. Perlman: Yeah, I agree with that. It's just that the additional studies, the best ones, may be really hard because it may involve parts of the-- May be assays we really can't do easily. So, I agree.

Dr. El Sahly: Okay. Dr. Monto, next

Dr. Monto: A point of information. I believe Novavax used a vaccine which was extensively tested without a safety signal, which failed the primary endpoint, didn't have a safety signal and did not use perfusion configuration of the virus. Do we know anything more about that? Because we're all-- It is a different platform with a different-- Which didn't produce the right antibody and did produce some protection, but not enough.

Dr. El Sahly: Is that the one in elderly, Arnold? Are you referring to the one in elderly?

Dr. Monto: No, I'm referencing the one that was in young children.

Dr. El Sahly: Okay. Yeah, I'm not familiar.

Dr. Monto: It was tested in multiple countries, South Africa where I heard from people there, they thought the protection was sufficient to introduce it, but it failed the clinical trial endpoint and therefore could not be approved.

Dr. El Sahly: Okay. Is this data public domain as far as anyone knows?

Dr. Monto: I believe they are.

Dr. El Sahly: Okay.

Dr. Monto: It's just a question of mine not being able to speak to this, and I wonder if people from the FDA would be able to give us some commentary about it.

Dr. El Sahly: Anyone from the FDA familiar with the clinical trial referenced by Dr. Monto?

Dr. Kotloff: Is this a maternal vaccination or an infant?

Dr. Monto: No, it was a child vaccination.

Dr. Beeler: Novafax-

Dr. Monto: -No, excuse me. It was maternal vaccination.

Dr. Beeler: Yes. [Indiscernible - 2:28:28] You're absolutely right.

Dr. Monto: -My mistake. Okay. Sorry.

Dr. El Sahly: That's been released.

Dr. Monto: Now you mention it, it comes to mind.

Dr. Beeler: That one's published. There was no-

Dr. Monto: That was published. Yes, it was.

Dr. Kotloff: Yeah. And it's about 40%-

Dr. Monto: 40%

Dr. Kotloff: Efficacious.

Dr. Monto: Right. But no safety signal.

Dr. Kotloff: Yes.

Dr. El Sahly: But it was in mothers.

Dr. Kotloff: In Mothers.

Dr. Monto: In mothers, absolutely. My mistake.

Dr. El Sahly: And they met the secondary endpoint, but not the primary endpoint

Dr. Monto: If it failed the primary endpoint. But I think I really do believe that other confirmations need to be examined. This is such a complicated problem. I don't believe we'll be able to really predict very well what's going to happen in human use.

Dr. El Sahly: Doctor-- Thank you. Dr. Portnoy.

Dr. Portnoy: Great. Thank you. Oops. Trying to get my video to turn on. There you go. Yeah. I'm really heartened to hear that we're making so much progress in the development of RSV vaccines. Every year, Children's Mercy Hospital where I work fills up with infants who have bronchiolitis. It's the number one cause of hospitalizations in infants. We're staffing up right now in preparation for this year's event. It's just a major problem. And the fact that we're making progress in vaccines is very heartening to me. I'm particularly interested in risk factors for patients who have either adverse reactions after the vaccine or even develop severe RSV in general, because I'm thinking about the Tucson study where all infants were enrolled in a large cohort and then they were followed over time to see if there were things that predicted who was going to have severe RSV infection. And what they found is that there were certain risk factors that predicted severe RSV infection. Some of these infants actually had increased airway hyperresponsiveness at birth. They had increased evidence of Th2

immunology. They had atopic dermatitis, they had a family history of eczema. There were things that predicted it. And those were the infants who had severe RSV disease.

And I suspect that those same patients would be the ones who might have enhanced infection after getting the vaccine. And I think it's really important that we look at these risk factors to determine whether something predicts adverse reactions, because if we can identify those individuals and maybe do something different with them, all of the others who don't have those risk factors could go ahead and get the vaccines and not be at risk of having this enhanced respiratory disease. So, I think it's really important that we look for risk factors for this. In fact, I remember one study where our IgE was developed to RSV. The patients literally became allergic to the virus. Maybe that's part of why they had so much trouble.

My other concern is whether getting vaccinations to a large population can reduce the risk of spread of RSV. Right now, RSV is so prevalent, everybody gets it. But if enough people become immunized, is it possible to reduce the prevalence of RSV so that you have a lower risk of actually being exposed to it, kind of herd immunity? Is that something that can happen? Do these vaccines reduce the risk of spread or do they just reduce the risk of disease, but you're still spreading it like the way COVID vaccines seem to work? Those are issues that I think need to be explored and looked at.

The idea of giving passive immunity followed by active immunity sounds really good. If we want to give injections, and we were worried about a problem with enhanced disease, it looked like the kids eight months and older did fine. It's the one when you tried to go to younger ages. Maybe you give passive vaccination and don't start the active until eight months just to keep it safe. Those are just some of my thoughts.

Dr. El Sahly: Okay. Very good. Thank you. Dr. Long.

Dr. Long: Yes. Hi. I want to reflect on a few things people have said on-- First of all, the unmet need. 3.9 million infants were protected by either maternal immuno-- Were potentially protected by maternal immunization or the more common of them by nirsevimab. And we know nirsevimab efficacy- Effectiveness so far in preventing hospitalizations in the first six months of life is 90%. We don't quite have that data yet for maternal vaccine, but we should have it relatively soon. The early graph of the age at hospitalization that was shown by Dr. Dawood is very important because the risk begins at three weeks of age- two to three weeks of age, and it's most prevalent the highest incidence is at two and three months, and then it begins to fall. And you saw that in the old data by the time you were into your second year of life, 12 months of age, it was not 2% who were admitted to the hospital, but it was 0.2%.

I really think that we need to have those data looked at again about who are those potentially vaccine candidates that are a little older that could benefit from vaccine because we know that respiratory infections and parental vaccines don't do much for prevalence of the organism or protecting the herd or the community. I think we have to be very honest with what the goal of vaccination would be, and it would be to prevent severe disease as it is now of the monoclonal antibody and the maternal and deaths that are predominantly in the otherwise healthy population and predominantly in the first 6 to 8 months of age. So, we would have to see if these vaccines-- I think it's going to be a very long time before these vaccines could be potentially given to very young children. And even if they were very young, I mean it would almost have to be newborn to protect that early group. I do believe that we will have a long and beautiful history with nirsevimab.

We did some due diligence about resistance. And of course we don't have a whole birth cohort having been given nirsevimab, but there was not a significant increase in resistance at the end of the children, the infants on monoclonal antibody experience. And monoclonal antibody as opposed to maternal vaccination goes well beyond six months. They only filed for six months. They only gave data for six months. But we know by looking at the decay of antibodies from nirsevimab, it's different from maternal, but from nirsevimab, that would go well into the second half of the first year of life.

The other thing that we didn't even talk about today, that is another oddity of RSV vaccines is-- Well, first of all, it only protects probably for six months. But the second part of it is that in older US citizens who were studied in the early groups before licensure of the vaccines in adults, they did not boost at six months. They did not boost at 12 months. They did not boost at up to 24 months. So, there is a bizarre second kind of a problem with the RSV vaccines that we have to date, that they have an unusual immunologic handling that would make me concerned.

And then for the attenuated, God love them. It sounds like a great idea, but it would be very difficult to figure out how old an antibody protected baby would have to be before you would be able to give a live-attenuated. And then would that have enough clout in preventing enough disease?

The last thing I'll say is what we learned during the COVID experience was that there was a dearth of RSV infections and all the studies were very under populated because there just weren't any hospitalizations for RSV. And what we learned in the year after that is, although there was a surge in those immunologically indebted babies who hadn't got their primary infection when it was occurring after the age of 8, 9, 10,

11 months, it was not as likely, even though it was primary, it was not as likely to lead to hospitalizations or severe disease. So, I think we need to re-look at all of that so we would understand the benefit as well as the potential risks, which are really, really something to think about now that we've seen the data today that they're not predictable.

Dr. El Sahly: Thank you. Thank you, Dr. Janes.

Dr. Janes: Thank you. Thank you, Hana. I wanted to reflect on the questions asked here, agreeing with others, it seems very clear to me that for the Moderna vaccine data that were shown today that there is evidence of a safety signal. So, I'm reflecting on the second question of what safeguards- what additional safeguards might be put into play as additional vaccines are investigated going forward. And I think the Moderna experience really highlights what was done well in this program and the importance of randomization and blinding and a placebo control, and the importance of essentially continuous safety monitoring to detect an adverse safety signal as soon as possible. And again, it seems to me that those were done very well in this situation and obviously should be carried forward to any future vaccine programs and vaccine research.

The only other attribute of the design that I could think of as it's been highlighted, we really wish we could understand better what participant characteristics and immunological features would predict the development of a vaccine-associated severe disease event. And one of the barriers to doing that investigation in the studies that we were talking about today is that a number of the adverse events happened before the blood draw to measure the vaccine induced immune response. I'm just wondering whether in future studies there would be value, at least in some participants, in staggering the immunizations relative to the RSV season so that the vaccine induced

immune responses could be measured and deeply interrogated before any clinical events occurred. And I don't know the practical considerations around that. Thanks.

Dr. El Sahly: Thank you, Holly. Dr. Monto.

Dr. Monto: It may be off the topic, but is the fact that this is being, the severe illnesses on challenge are occurring with the human metapneumovirus, is that telling us anything? Is that something that it's a virus that we know very much less about and one which we do not have passive immunization available? Should we be concerned about that in terms of this particular platform?

Dr. El Sahly: --I would think so. I mean, three out of 27 vaccinated with hMPV would be off the charts when it comes statistically speaking to historical experience. Right?

Dr. Monto: Yeah, it sounds like it. And it's something that's quite troubling.

Dr. El Sahly: Yes. And there also there is less information because these cases, as I understand, came in later, so we know even less on their immune response and antibodies, et cetera.

Dr. Monto: Right.

Dr. El Sahly: Yeah. Okay. Dr. Malloy. Is someone from Moderna trying to answer something?

Dr. Snape: Yes, if possible. Just to interject. Matthew Snape here at Moderna. I thought it would be useful to comment on the hMPV cases and to remind the committee that hMPV is another pneumovirus. It's very similar to RSV as a virus, and the F proteins themselves have a lot of similar characteristics. So, there's some overlap there, but it also does potentially give us the opportunity to explore baseline immunity

before these children got sick. Because as was being mentioned before about staggering RSV seasons, in effect, we have created a staggered season here because we've had an RSV season and now we've had an hMPV season, so we will have immunogenicity data at one month after the second vaccine before the children got sick. It's just that we don't have that data yet. And that will allow us to interrogate what baseline immunity looked like in the children that got sick and those that didn't get sick, and see if there's any difference there.

And just to say one more thing, it's about the distribution of cases. There were three in the RSV hMPV participants, and there was actually one co-infection with RSV and hMPV in a placebo participant just to, whether that would be RSV or HMV that made them sick is obviously it's hard to tell.

Dr. El Sahly: So what is your best estimate on the ETA of all these data? Are we talking three months, six months?

Dr. Snape: The hMPV data will be weeks. Yeah.

Dr. El Sahly: Weeks and then everything else that, you know--

Dr. Snape: Weeks for availability. And then we need to analyze it and QC and all those kinds of things, of course. But I think in general we should be thinking 2025 for these data coming through.

Dr. El Sahly: Okay.

Dr. Snape: Hopefully early rather than later.

Dr. El Sahly: Alright, thank you. And I don't know, this is something to the FDA colleagues, is that depending on what this data show when analysis is done on these

cases, it may inform the answer to the discussion topic a little better, right? There's quite a bit of unknown so far. I'll go back to Dr. Malloy. Thank you for waiting, Dr. Malloy.

Dr. Malloy: Hi. I just wanted to say that we know that RSV is very much a mucosal infection, whereas influenza and SARS-CoV-2 tend to infect outside the mucosa. And as we think forward, the data so far suggests that mucosal antibodies and mucosal T-cells can be supportive in protection against infection. And the consideration for adding some of these to our guidelines for how we're deciding safety and efficacy for some of these vaccines would be fantastic. And so, while T-cell in the mucosa are difficult to test, we've gotten so much smarter at looking at mucosal antibodies for both IgG and IgA and adding those to platforms for how we're designing safety and efficacy endpoints might be really useful for these vaccines as they move forward. And even in the idea of nirsevimab, if we can look at what the mucosal response is, do those kids that do well with nirsevimab have a higher mucosal immune response or antibody response would be really helpful. So, taking that as a sort of place where we might gain some more information about how we would look at the efficacy and safety of some of these might be really useful in these platforms that we already have and endpoints that we could already look at.

Dr. El Sahly: Well, that depends on whether the sponsor collected nasal washes or nasal swaps or--

Dr. Malloy: Yeah.

Dr. El Sahly: Thank you. Dr. Berger.

Dr. Berger: Thanks. I just wanted to follow up on Dr. Jane's comments and really focus on question two a little bit, which is asking what additional safeguards need to be put in place. I want to really stress the monitoring here worked. This is exactly what we expect and want to have happen. The safety signal was identified, the sponsor halted the study. This is exactly the type of safeguards you want to see happen. So, I'm not necessarily sure that there's additional safeguards as opposed to additional evidence needs. As Dr. Gans was noting on the front end of this session or this part of the session itself. I do think it's important to understand what that evidence base is around natural disease so you can have that comparator for understanding the immune response that's elicited naturally versus vaccine induced. I think all of that, just taken together, I think what is already in place is working. I think we just don't really have a good understanding of the mechanism that is driving the safety signal.

That said, I mean I do think there's a couple of good things that I just want to highlight. It looks like there's a possibility of having a vaccine that could be developed here. We see at least in "1a" live-attenuated doesn't seem to have any of these issues. That's a good sign for development processes. What kind of prompted me to ask the question I asked earlier in the day though, is about those other 11 clinical development programs. And I think this might be the one area that could potentially be more helpful for us because it's great and I'm thrilled to see that Moderna came forward with this and has been willing to be so open about the study itself. Not understanding what's going on in those other 10 though it's hard for me to make a judgment that it's a platform issue, and so I can only make a judgment based on the one study I'm seeing.

I think it'd be great to have some additional measure that allows for better understanding while those studies are ongoing, if they're seeing signals that we can combine. Because I get the sense, at least from the way this question is phrased in "1a",

it's looking at technologies and mass, and I don't think we can make a generalized answer to a technology based on just having one study. I fully agree there's an absolute safety signal here and the steps that we're taking I would support, but I'm not sure I can actually apply that to all mRNA programs. So, going back to what Dr. Monto had said, Monto had said early on, I think we do have to look at these at a platform basis, but at this point I think we need to look at them at a platform basis and a per clinical development program basis unless we can get better coordination of being able to get evidence from those other programs that are in developments. And I recognize that there's issues in terms of confidential information sharing and whatnot, but I do think that's the one gap that I'm missing to be able to answer "1a" well, which is that generalized vaccine technology platform question. So, thanks.

Dr. El Sahly: But would you agree, Dr. Berger, it's that the predictive model that we are using, which is largely based on what happened with the formalin inactivated vaccine and how we understand the immunologic basis of the enhanced disease there. So, we took what we learned from that particular incident and we applied it and established the safeguards whereby all other platforms should move, right? age de-escalation, Th1, Th2, the histopath upon rechallenge, all of these safeguards were put in place. Looks like the vaccines are passing these initial safeguards and however, once they come to the relevant population, it seems that these safeguards did not really predict the outcome. You know what I mean?

Dr. Berger: Yes. And I think that's why I was noting earlier and agreeing with Dr. Gans's points. We need better evidence about what's actually driving the immunological response. The general safeguards that are put in place around the clinical studies themselves seem to be working. We're identifying that there is a safety signal and halting the study. What we don't have a good handle on is the evidence-based or the

evidence that's driving that ideological difference here. And we take what we're learning from the past, but I think we are missing a bit to understand what's going on currently with these newer types of technologies that are being employed. I'm just not sure I can apply it across the entirety of the technology. I don't know if all mRNA programs are all going to have this problem or not. That's really my point that I'm trying to make. I don't know if I can extend that to all of a specific technology as opposed to a particular clinical development program until we have better evidence around it. That's why I'd like to see better coordination or collaboration around driving that evidence base between clinical development programs and also having a better evidence base about what's actually happening in response to natural disease so we can understand the vaccine-induced immunology.

Dr. El Sahly: Karen, if you can wait just one second because we have two experts who can speak to the natural infection, immune responses and answer, potentially, some of Dr. Berger and Dr. Gans questions. We have Octavio Ramilo and Tony Piedra. If I can ask one or both of them to weigh in on gaps in knowledge pertaining to protective immune responses after natural infection. We have Tony and we have Octavio.

Dr. Piedra: Octavio.

Dr. Ramilo: You go for it, Tony.

Dr. Piedra: Sounds good. So an area that was mentioned that we have basically very little knowledge of is resident T-cells and what's happening in the lungs or in the mucosa. We don't have evidence or good information on infants or young children following RSV infection. We have it more on adults who undergo the experimental challenge with RSV. But this is an area that is, I would say, needed to better understand down the road. We are getting now with newer technology, a better understanding of the

type of antibody repertoire that infants develop with primary infection and is oftentimes age dependent and whether it's under or after the umbrella of maternal antibodies. And nirsevimab is going to be, I think, a very important question to address as well where it may look different from maternal antibodies, even though maternal antibodies are going to be high in antibodies that target the prefusion sites.

So, I would just say that in infants, the antibody response and repertoire is quite different from that of an older child or an adult and you don't have the same level of avidity and you don't have the same broad repertoire that occurs in individuals with repeated infections. And so with that, the cellular immune response, I'm less informed other than what I read and Octavio can probably shed additional light. What I will say is that the innate immune response, we know a bit of the type of response that we see following infection in infants and toddlers. Octavio has developed a bit of that information we have as well. And it kind of goes initially against the paradigm that a very, let's say robust or exaggerated cytokine response was detrimental. What we have observed in others is that an early robust response- Cytokine response that is associated with innate immunity actually plays a favorable response for the host in, I won't say clearing viral infection, but in ameliorating disease severity.

Dr. El Sahly: Thank you, Tony. Octavio.

Dr. Ramilo: Thank you for the opportunity. My name is Octavia Ramilo. I work at St. Jude Children's Research Hospital and our research group has been working on RSV, especially in infants for the last 25 years. So, thank you for the opportunity to contribute to the meeting. We have a very incomplete understanding of RSV immunity despite 60 years of research. I've been brought by the DSMB committee to help understanding these findings. So, I've been exposed to this data for the last month and a half. And

obviously the first thing is being humble because everything we thought we knew about how to make a vaccine and how to leverage the animal models to understand what happening in kids, it was incomplete. That's very important. And the history of RSV has always been like this. We take us-- Unless we do a very scientific driven approach, our ability to protect and develop protected aspects against RSV has been very limited.

Now, if I may, it's important that we use markers of protection, pref antibodies and neutralizing antibodies, but we measure them in the blood. The virus infects the upper respiratory tract. So, Dr. Malloy mentioned we should focus more on what happens when the virus infects through the mucosa. And I think it's going to be very important. It has been suggested by a number of the Committee that maybe a suggestion that is not too complicated is to include measuring of mucosal antibodies in the context of these vaccine trials. We know, we haven't published this yet, it has been presented in meetings, that young infants we can detect in the mucosa maternal antibody, it's totally IgG, it's not IgA. After they develop the response, the IgA is really high and the IgG as well in the mucosa, but this is age dependent. My colleague Dr. Mejias and I have studied very carefully the age effect on development of antibodies in the natural infection and in the first few months of life, the response is very weak. It begins to be a bit sustainable, I'm talking about preF and neutralizing antibodies, after six months with natural infection.

So, it's going to be difficult because the vaccine, whether it's mRNA vaccine or live-attenuated vaccine, we want to be better than the natural infection. And because the natural infection is really bad. Looking at the innate immunity, we found out that the innate immunity you are under six months or after six months is totally different. The interferon response is so limited that number one under six months, it does not protect the acute situation, but probably does not help telling the B cells what to make a more

productive and effective response. The third, Tony alluded to the paradigm of understanding how viral replication and mucosal cytokine response protect or not protect. 25 years ago, we were convinced that the kids who got in the ICU were hyper inflamed. Now, there is a lot of data suggesting that actually the innate immune response is weak or disorganized.

We learned that if you have a lambda interferon or IP-10 in the mucosa, you're well protected. But if you have IL-6, you tend to be more hospitalized. So, understanding how the regulated immune response works and how our vaccines can develop such a protective response is going to be very important. I really encourage that we incorporate more immune profiling for me to say from academia and what is doable. Because the challenge is how we enroll kids and we are not too aggressive about collecting too many samples, but maybe in the mucosa it can be done.

Finally, there's another paradigm that Dr. Piera has seen and we have seen that when we think about viruses and we talk about CMV, HIV, hepatitis C in the blood, the correlation between viral titer and disease severity is clear. That's not the case in RSV. We see that kids hospitalized with RSV have lower viral load than kids who are managed as adult patients. So, it's another paradigm understanding how viral replication, the immune protection in the mucosa, I mean the immune response to the mucosa, both innate and adaptive, play a big role.

I think there are a lot of gaps in our knowledge and, if I can complain, there's very little NIH funding to study RSV natural infection for the last few decades. Some of the members of the committee will [Indiscernible - 3:00:21] that. So, my advice to all the colleagues who are passionate about developing an RSV vaccine, and it's important to remind that from six months to two years, after six months you can have half the

hospitalizations. And I mean Dr. Long was alluding what is the landscape. And you too, Dr. El Sahly. And I think it's important to realize that a lot of the morbidity that occurs, even if it's not hospitalization, is very real and causes long-term implications for their way and long-term sequela. So, I don't think we should be happy to just prevent hospitalization. Thank you for the opportunity to contribute to this meeting.

Dr. El Sahly: Thank you, Dr. Ramilo and Dr. Piera. Back to Karen.

Dr. Kotloff: Okay, thanks. Thanks, Hana. I just wanted to emphasize that there seems to be a green light if I'm understanding it for the live-attenuated vaccines. And I think one very important step is that we need to have a good safety base for kids who are seronegative that don't come in with good immunity from their moms because we may have a false sense of security. And then also, I think it's true that the guardrails worked in terms of detecting the severe cases, but they didn't work obviously in predicting what those severe cases are. And I think that that should be an area-- And I think we just heard about that and it was really good to hear about what we know about pathogenesis. And I do think that we learned for pertussis that there's a very characteristic pertussis lung that's associated with mortality, very characteristic histopathology. And I do think that the kids who die from RSV are also different and understanding the immune profile in response to vaccination and in response to infection, better understanding that would be very important in helping us to understand the safety of vaccines.

Dr. El Sahly: Yes, great point. Thank you, Karen. Dr. Gans.

Dr. Gans: Thanks everyone for this amazing conversation and Octavio for coming on and sharing with us the immune responses. I just wanted to caution people to be very-- Again, I feel like we can access antibodies and we do them very well. They're not the whole story. And if we're going to get anything that actually is an immune

profile that we really want to see, it has to be robust. There is data that even in the presence of maternal or any passive acquired antibody, that T-cell function is actually fine, while there may be differences in humoral immunity. So, there's a little bit of a disassociation, and we can't just say that because we have one, we actually have the other. I think we need to be very careful in infants how we're looking at both of the arms. Well, including innate immunity as Octavio has really well identified because all of these are limited in different ways. And I think it's very much the way that natural immunity is supposed to be acquired over time so that it's not actually too robust. It doesn't cause tissue damage. It's limited in a way that actually is probably pretty biologically sound. And so we have to be very careful about that.

But I also just want to dispel the notion that you can't immunize infants in the presence of passive antibodies. I mean studies that have been done in the context of that and the developing world have actually shown that, for instance, measles immunization, same type of process that would inhibit humeral immunity, actually is a survival advantage for those infants, not only in terms of measles disease but just overall survival. So, there are many ways of looking at this and I think we need to not-- We know that antibodies can prevent the virus from actually attaching to the cell. We know it's good for the extracellular. These viruses have many different compartments that they actually infect, and we need the full immune system to actually be present for us to actually be able to handle these viruses.

I just want us to be comprehensive rather than myopic about not only spaces, we've already said there's lots of lymphoid tissue that's within our respiratory tract. We should be able to do nasal washes on children who are in, if we want to look at immunity, we can do these now on small sample sizes. We've really progressed in our ability to do that. We don't always have to just work with PBMC. I think there's just a

lot of also immunologic diagnostic advantages that you can do on small samples and that shouldn't be restricting us at this point in time. I really appreciate the conversation. I just wanted to add those points.

Dr. El Sahly: Great. Thank you. Dr. Nelson.

Dr. Nelson: Yes. Thank you for giving me the opportunity to comment on these discussion items and be a part of this conversation. It's been very enlightening. And also put a plugin for the appreciation to Moderna for being so transparent and volunteering to present their data to this Committee for their adoption. What I would like to state is that I too agree that the system worked, the safety signal was reached, a proper pause was put in place. I'm not totally convinced that the finding of the safety signal means that the signal is real, and the reason is that for some of the reasons that have been just articulated over the last hour, we haven't achieved enough understanding of the exact immune response of study participants. And in particular, I don't think we've learned enough from those who experienced the severe adverse events and some more attention to be investigating what happens to them in real time, I think could be incorporated in future clinical trials as well.

So, the safeguards that this Committee and the FDA recommended and put in place actually I think did work. I think we need to put a little bit more emphasis on the understanding of host factors. I mean, this is a unique situation and with RSV age de-escalation, we were actually headed into a headwind of Th2 bias, which we know exists as most prominent in the younger age groups. In addition, I noted that for Part B of the Moderna trial, it was conducted entirely in Panama. And we do know that there are ethnicities, genetic and epigenetic and environmental social determinants and health factors that can impact the immune response of individuals. Yet I don't think we've

understood or even asked the question about the participants in these trials and how generalizable they are. That's not at anybody's fault, but should be a future thought process as we conduct and design future clinical trials. I think there's the opportunity to learn more about our participants in these trials before the intervention and to certainly assess in more detail what happens afterwards.

I'll put in one other plug on 1.1a with respect to platform. As an Allergist Immunologist, I'm always concerned about our population that has inborn areas of immunity and primary immune deficiency. So, yes, newborn screening has certainly unearthed and identified or diagnosed kids at a much earlier age, but there are multiple conditions that don't come to life until later. Most live vaccines with the exception of rotavirus, are held off until one year of age. As we look to introduce live viruses into children below the age of one, that risk to this undetected population does increase. So, really identifying the proper risk factors and being able to screen out those at risk from a live-attenuated platform, I think it's going to be essential. Thank you.

Dr. El Sahly: Thank you. Clarifying question to Dr. Connelly or to Moderna. Are all the severe cases in Panama? I thought that was the hMPV and the other ones were mixed.

Dr. Snape: It's Matthew Snape here. I can talk from Moderna. All of Part B-- There were 81 children recruited to Part B. 80 of those were in Panama and one was in the UK. And so all of the children that got sick were in Panama given-- In B. This was planned as an international study, I mean as many of these vaccine studies that are done for seasonal viruses are planned to be done across hemispheres. We're going to be recruiting-- To respond to one of the questions earlier about them all being in Panama, actually, we actually had approvals to be doing this study in eight different countries as

it happened the way the RSV seasons worked, that Panama was the one that was in the best place to recruit at that particular time.

Dr. El Sahly: Okay, got it. Thank you. Dr. Meyer.

CAPT Meyer: Yes, thank you. I agree. This has been a really great discussion, a lot of great points by my colleagues and I don't have too much new to add. I just kind of wanted to summarize my thinking around this issue. I think my takeaways from today are that we had some very well thought out safeguards put in place that were based on prior experiences of vaccine candidates. Multiple global groups looked at this issue, all came to kind of similar recommendations around how to study these vaccines. This was a very well thought out process. But again, as others have pointed out here, we are talking about a safety signal and we don't really understand the mechanism why. So, for me, it makes it very difficult to comment on the second question about what additional safeguards or what new ways to study this we can put in place without really understanding what we think may have happened here or why the safeguards we put in place didn't necessarily predict severe outcomes.

So, I'm really hopeful that some of the additional investigations that Moderna has discussed can shed some light on this and some of the other studies that my colleagues have recommended. For me, it makes it very difficult to really comment on that one.

In terms of the first question though, I mean I'll add my input on this. I do think we saw some data presented today during the Open Public Hearing around the live virus vaccines. And I think if I understood our Sanofi colleagues correctly, thousands of children have already received a vaccine in those trials and not found a safety signal. And I found that reassuring because where we have detected safety signals, it's been in

pretty small numbers of kids. And so, I think that was good signs that we can develop that there are different vaccine technologies that may have different outcomes. I think I would agree that we need to look at these and yeah, that's what I'll add at this point. Thanks.

Dr. El Sahly: Great, thank you. I'm going to go through the participant list, make sure I heard from everyone and if I didn't, I'm going to call your name, sorry. That would be-- Where's the list? Okay, so that would be Dr. Offit and Dr. Bernstein. We didn't hear from either. Did I miss someone else? No, I think everyone else weigh-in.

Dr. Offit: Sure. You want me to comment? Can you hear me okay?

Dr. El Sahly: I can.

Dr. Offit: Yeah. So, I agree with what's largely been said. I think the frustration in this is one, this involves a handful of children. Two, the things that were in place that we felt were predictive regarding formal-- Formalin-inactivated vaccine, or formalin-inactivated whole virus. And this sort of pre versus postfusion protein doesn't seem to apply here. So, we're not sure what applies here and I'm not sure how much we're going to learn moving forward. We certainly were right to stop the trial. So, having stopped it, I'm not sure how much we're going to learn moving forward. It is a little frustrating. I mean, it is possible. This was brought up by one of the commenters that this is just a spurious association. I mean we in the rotavirus vaccine trials for example, which was a prospective placebo-controlled trial that involved 70,000 children, there were nine cases of seizures in the vaccine group two in the placebo group, which was statistically significant but didn't hold up. And there were five cases of Kawasaki's disease, the vaccine group, and none in the placebo group that was statistically significant but didn't hold up.

So, sometimes there's a tyranny of small numbers, although of interest there were five cases of arm and leg fractures in the placebo group and none in the vaccine group, which is to say the rotavirus vaccine prevented arm and leg fractures. I don't think Merck got an indication for that. But in any case, this is the problem with small numbers. So I do, I'm a little frustrated by the fact that one, I don't think it's clear what the pathogenesis of this is, and two, it's not clear to me how well we're going to learn it moving forward. But that's all.

Dr. El Sahly: Thank you Paul. And Dr. Bernstein, if you don't mind.

Dr. Bernstein: No, of course. Sorry about that. But first of all, I thought, well the presentations and the discussions were quite educational for me. I thank all the speakers and people around the table. I mean this all seems like an incredible conundrum with lots of unanswered questions remaining. So, lots to still learn. Indeed there does appear to be a true safety signal in young children. And I did wonder, just as Dr. Nelson and you, Dr. El Sahly, said. I wondered about the fact that all the children were from Panama and not in the United States or elsewhere. It does appear we need more studies of potential vaccine candidates by platform and pediatric age groups and by more than one RSV season. It's particularly confusing to me what the additional benefit is for a pediatric vaccine in children under a year, given the availability of antepartum RSV vaccine and nirsevimab.

On a related topic, I think it'll really be important to determine how vaccination of pregnant women with each pregnancy as we do with Tdap impacts RSV epidemiology in young children. And I was concerned about the addressing of decreased monoclonal antibody effectiveness with the possibility of mutation as one of our colleagues mentioned. And I guess I'll end with the fact that this meeting and its

presentations, and all these robust discussions highlights very well how valuable science is in making an incredible difference in public health. And we hope that that message comes across loud and clear going forward. Thanks.

Dr. El Sahly: Thank you. So, I think-- Any other hands? Dr. Monto.

Dr. Monto: I will follow up with Dr. Offit's comments. Being an epidemiologist, I'm always afraid of making conclusions from small numbers. However, we also look at biologic plausibility and when you see this kind of situation with both RSV and human metapneumovirus, I think it's plausible that this is a real event. Now, we're not-- Given the fact that our predictive models haven't been working, the problem is either we go forward very carefully with clinical trials where we may be able to get an answer or we continue to observe natural infection in which over 50 odd years we haven't really been able to identify anything that would help us in answering the questions that are currently being raised. And that's one of the reasons why I believe that it is important to continue and to cross pollinate, as Dr. Berger said, so we get some better predictions of what will happen and gather numbers. So, we're convinced that they are happening and we do not just shut down programs over the current findings, real though they are. Thank you.

Dr. El Sahly: Thank you, Arnold. But we have to-- I mean, shutting down programs of course across the board is not the goal and that's why we're meeting,

Dr. Monto: I know that's why I'm saying this because we heard from Moderna that they are changing their goals.

Dr. El Sahly: Yes, but the other, on the flip side, there's the issue of risk benefit human subject.

Dr. Monto: I understand. The dilemma is that we don't know how severe the severe cases would be if we continue to evaluate the vaccines. So, it's a very hard decision and that's why we're being asked the questions that we're being asked.

Dr. El Sahly: And the final comment is from Dr. Janssen before I try to summarize the discussion

Dr. Jenssen: As an epidemiologist also, it's a potential safety signal, but I think it's absolutely the right thing to do and not at all surprised by Moderna's decision. The question is how did the other programs get off clinical hold. And I really haven't heard anything offered different that would allow them to get off hold unless the FDA decided to go ahead platform by platform. Also, I think the other thing to consider is the route of administration may matter as was mentioned earlier. I think the one thought I have, I'm an adult physician, I'm not a pediatrician. I haven't done enough studies XUS to comment on medical care in Panama or other countries. But potentially it would be important for FDA to require studies being done under IND, to be done in the United States with access to children's hospitals. It's the only thing I can think of without adding anything else here.

Dr. El Sahly: Thank you so much. Okay. So this was a rather involved and very stimulating discussion to a very, I guess, vexing question, given the small numbers, the data being not finalized in terms of the evaluation of these adverse events, et cetera. The sense of the Committee that these potential safety signals, although small in numbers, however, RSV associated severe LRTI and hMPV severe associated LRTI in an hMPV/RSV vaccine is rather compelling as opposed to the fracture or the Kawasaki. So, the potential safety signal, especially in the history of the 1960s is rather compelling that the signal is likely true but not final, but likely true and should have been addressed

with the urgency that it was addressed with in terms of the sponsor and in terms of the FDA.

The Committee after review of the data of the mishap or the tragedy of the 1960s, the predictive model was followed however, did not really predict what the outcome would be once the vaccine moved into the seronegative infants who do have a predilection of differing immune response with potentially a Th2 bias in general. What does it mean for different vaccine technologies? Certain technologies like the live attenuated have a track record in the thousands already and within various, I guess, minor changes to the constructs and in various medical institutions or centers. So, there is a reassurance that potentially it can carry its own weight, so to speak, given the existing data and moving it forward would be, I guess, less anxiety provoking than subunit vaccines.

Subunit vaccines have been tested in humans of all ages, whether it's the recombinant prefusion, the one that is just recombinant F, there were no safety signals in adults. A couple are already licensed, but to my knowledge, none were in seronegative infants. How do the events of the last few months change what needs to happen for these particular vaccines to go into that sliver of the population? I am not sure. However, maybe the additional data that is forthcoming from the collected samples can guide-- If they do shed light onto what was different in the immune response there. Different antigenic confirmations are a little harder. The stabilized preF is the one that is in the constructs under consideration today. And it didn't seem to predict the preF/postF ratio was of course in favor of the preF, but it didn't seem to have abrogated this particular signal. And based on the currently available evidence, when it comes to the clinical information, for example, the clinical trials that will be resuming, I'm assuming at a minimum they're replicating ones, the safeguards in place seem to

catch such an occurrence. I'm pretty sure all the DSMBs of those trials are on the lookout, even more so now. But what additional nonclinical information should be considered is unknown at this phase. It is something that potentially can be amended once more data from these infants and toddlers are forthcoming.

And then we touched upon the new lay of the land, which is to understand the risk benefit which all RBS need to know going forward when they review these vaccine studies. We commented that this is an evolving field and our colleagues in the CDC, and colleagues in the FDA who will see the subsequent seasons data from the clinical trials also will be analyzing those data. And this will also be informative of the risk benefit going forward. Did I miss any major or- Major issues? There were a whole slew of other great ideas along the way, but these I think are the highlights of the discussion. And with that, I'd like to move to Topic II or question 2. Topic I. We have, but just so everyone knows, we have 31 more minutes.

Sequential administration of RSV monoclonal antibodies followed by RSV vaccines in infants and toddlers. Please discuss whether currently available evidence suggests potential RSV mAb, such as nirsevimab, and there may be more coming down the pike, RSV vaccine interactions that may affect active immunization in infants and toddlers. And: Based on the currently available evidence, please discuss and recommend whether any additional factors and data should be considered when evaluating RSV mAb - RSV vaccine interactions, including potential impact of administration of RSV mAb on safety and or effectiveness of subsequent parental or mucosal administration of RSV vaccines.

I invite everyone in the Committee to use the raise-your-hand function to comment on this particular question. Okay. We have first Dr. Gans.

Dr. Gans: I guess I didn't fully realize there was a full question on this. Sorry to not prepare because I think we've already discussed it a little bit. So, I think--

Dr. El Sahly: Maybe some additional thoughts or--?

Dr. Gans: Yeah, so I think that one of the important components that comes into play when we're thinking about any kind of passive immunity and then trying to elicit active immune responses to a vaccine is that we need the full picture. So, I think we've alluded to not having a complete understanding of immunity under any of the conditions in which we're sort of thinking about, but particularly with this particular thing, because I have studied it, it really behooves us to understand all components of the interaction with the passive antibody and whatever antigen exposure we're giving, we need to know and innate and adaptive immunity in those circumstances. Typically humoral immunity is blunted, but it can be boosted with additional exposures and things like that. So, that's what has to be understood and it still should be considered a very viable option despite seeing slightly diminished humoral immune responses. I think that that's just part of the picture. We know very well that people who show that profile actually are protected against disease, particularly disease severity. So, we have that understanding from other antigens and that should be considered and studied further.

The only other thing I would say is, again, we have nirsevimab, which has been very impactful and wonderful and we do hope it stays part of our management for these individuals. Again, I think the question needs to be expanded to maternal immunization and that effect on not only protecting our infants in their early infancy in those few months, but then also how that impacts subsequent immunization of that pairing. That is something that we're interested in doing because of what was discussed earlier, the diversity of the immune response that the mothers can pass on to their infants not only

during pregnancy but also during if they choose to breastfeed and other ways in which they can continue to help protect their infants in an active immune if they are actively contributing to the baby's immunity. And then obviously subsequent immunization on the child's part.

Dr. El Sahly: Thank you, Dr. Gans. Dr. James?

Dr. Janes: Thank you. I'll be brief. I think I agree with a lot of what Dr. Gants just mentioned. To me, I don't think we saw enough data here for this vaccine to definitively establish whether or not prior passive immunization affected the immune responses induced by this vaccine. There were just insufficient numbers to answer that question. And moreover, the prior discussion really just highlighted the fact that we don't know really the full profile of what a desirable immune response here is in terms of inducing protection. So to me, this just really highlights the importance of this question going forward. And as Dr. Gans mentioned, both preexisting passively acquired immunity by virtue of antibody administration as well as passively acquired antibody from the birthing parent. Thank you.

Dr. El Sahly: Okay. So, when it comes to this particular issue, we have small numbers, nine infants who got nirsevimab, six infants who got no nirsevimab. They were both given the mRNA vaccine and those who were recipients of nirsevimab eight months prior, at least, I think the range was 8 to 12, had no increase in their RSV A neutralizing antibody titers or RSV B, for that matter. While the infants who had no nirsevimab at birth had a 60 fold increase in their nirsevimab, in their neutralizing antibody titers against A, and 19 against B. The numbers are small, obviously, as a result of the halt of the product development. And however, again, it is striking that there was absolutely a flat response. Having said that, it seemed that the nirsevimab-exposed infants did have

preexisting titers, so it is possible they did have-- Yeah, and they were neutralizing. So, it is possible that they are in the tail-end of their nirsevimab, they're still protected maybe, and we went and vaccinated them too early. So, there aren't enough permutations in the time to understand the role of-- The time of vaccination relative to the nirsevimab receipt. It is possible that this is a time-dependent variable, but could not be studied because the study went on hold as a fallout from that. So, we don't know how the time since injections is going to affect the response, but also what it means to other platforms that want to study their vaccine post-nirsevimab. Nirsevimab, again, this would be season two that it is administered and in season one there was a significant shortage at many medical institutions and healthcare providers.

So, the durability of the protection of nirsevimab remains to be seen, and it's waning and to how much-- It's possible that it all goes away, but maybe there's a degree of protection that remains afforded by this particular intervention that we need to evaluate as time goes on. And I'm pretty sure in a year we'll be having a different discussion around this issue. So, until we have those data, it's hard to extrapolate to what other manufacturers should do, etcetera. But at a minimum, having an understanding of when a vaccine would be needed given what we know about nirsevimab, what we will know about nirsevimab and other monoclonal antibodies, and the manufacturers, and the sponsors to take that into accounting in terms of the time variables and the population they will study. That's how I see Topic 2, and you will be asked to comment on it. So, be ready. And we begin with Dr. Monto.

Dr. Monto: I think the only certainty here is that the live-attenuated vaccine is going to have to be evaluated in terms of when it can be used. In the past, following the administration of the monoclonal antibody, the duration of protection that has been seen may actually force a delay in the use of the live-attenuated vaccine. In terms of what

we've seen with the mRNA vaccine, I wouldn't be concerned with the kind of blunting of the immune response that has been seen because the immune response was so robust. We don't know about the efficacy of the immune response given the small numbers and the safety signal. So, aside from pretty clear conclusions about the live-attenuated vaccines, I don't think we're in a position to really comment with any kind of certainty about the current situation.

Dr. El Sahly: When you say comment on the current situation, meaning the mRNA or generally speaking, when to administer?

Dr. Monto: I think it's premature to talk about that. I think it needs to be studied, and that's something that's fairly easy to be studied in the United States, and that's almost certainly why studies have gone outside the United States in order to be able to find populations which are not at least recommended to receive the immunoglobulin-- The monoclonal antibody, I should say.

Dr. El Sahly: Oh, okay. So, your comment is really in reference to--

Dr. Monto: I think that becomes one of the practical considerations in going outside the United States. And if we're going to say that the vaccine-- The trial should be done for safety reasons in the United States, then we have a problem in evaluating a significant number of children who do not receive the monoclonal antibody.

Dr. El Sahly: Definitely. That's a conundrum. However, I think here--

Dr. Monto: Yeah. Many conundrums.

Dr. El Sahly: Yes. The topic, I guess, here for Question 2 is specifically following nirsevimab, not how to avoid nirsevimab. Assuming somewhat the kid got nirsevimab, and so how do you maneuver that?

Dr. Monto: Well, yeah, but you'd like to have a comparator.

Dr. El Sahly: Yeah. Okay. Dr. Ruckwardt.

Dr. Ruckwardt: Hi. Yeah, so I guess I'll just weigh in on my thoughts on this one, which are largely as everyone else's. I think there's very little evidence here to base anything on, specifically for nirsevimab and the single dose of mRNA, which was all that was given here. But at the same time, I don't think it's too much of a limb to say that this would be expected, this blunting would be expected, and there's not any evidence here of a safety issue in this small group of infants. So I think we couldn't-- It's premature to speak about the safety issue, but I think as for the first point, this would have to be evaluated on a platform by platform basis, and based on what we already know, we would expect that this kind of blunting would be probably less apparent with some of the mucosal vaccination approaches. Thank you.

Dr. El Sahly: Great. Thank you. Dr. Berger?

Dr. Berger: I agree with what all has been said. I just wanted to add one additional piece. We also don't know if the blunting would've been even less if we had gone through all three of the doses that were given here. It is just hard to make any definitive decisions or conclusions based on a total of 15 research participants in the study that didn't even get to administer all of the entirety of what was meant to be administered. So, I would be really hesitant to make decisions at this point on this without collecting more additional evidence. Thanks.

Dr. El Sahly: Thank you. I don't see any raised hands, so I'm going to use-- I'm going to ask everyone to weigh in however little or a lot you want to say on this particular topic. And I'm going to go in the order of appearance on the participant list here. Dr. Malloy?

Dr. Malloy: Hi. I think just as everybody has pointed out, we lack really robust metrics for what's a correlative protection. So, we'd be hard pressed to say exactly what nirsevimab is blocking when it's blocking something other than this idea of the peripheral sort of preF antibody response. And so, I think more data is required to really weigh in on when or if you would have to limit the use of a RSV vaccine. And again, it would have to be based on each platform and how it works. So, I think all those things would-- We just need more data in order to understand what we would really need for prevention of RSV and then what the correlates of protection are so that we can use those as metrics to decide whether nirsevimab has to be held or waiting after a nirsevimab administration in order to do that.

Dr. El Sahly: Thank you. Dr. Bernstein?

Dr. Bernstein: Yeah, I mean, nirsevimab may have blunted the immune response, but really in a very small number of patients, and there really are not enough data, as others have said, to draw significant conclusions about RSV vaccination of infants who received nirsevimab. I think that, and agree, that this should be studied by vaccine platform and also the number of doses received by the children.

Dr. El Sahly: Okay. Thank you. Dr. Janes?

Dr. Janes: I don't think I have any additional comments on-- I feel like this is an important further question. We don't have sufficient evidence to make determinations on the answer at this point.

Dr. El Sahly: Dr. Portnoy?

Dr. Portnoy: There you go. Yeah, just thinking about vaccines in general and children who get vaccines, as newborns given vaccines for diseases that they're not likely to catch right away. RSV is almost an emergency. This affects infants at the very earliest of ages, and so they need to be protected right away. While it would be great if we could actively immunize newborns with an RSV vaccine, I think passive immunization is probably the best solution at this point because these infants need to be protected immediately. They're at risk of severe disease right after they're born, if they're born at the wrong time of year. So, the idea of sequentially giving passive immunization and then waiting until they're a little bit older before giving the active vaccine makes good sense. I've seen evidence that it seems to be very effective. There may be some infants who don't respond as well, who may have enhanced disease as a result of the vaccine. I think that those infants probably are different than the other ones, and that there are maybe risk factors that can be identified that could potentially identify who they are and maybe modify their treatment, have them avoid getting the active vaccine. I can't think of a better way of protecting infants from bronchiolitis, which is the clinical disease that they get from RSV other than passive immunization, either from administration to pregnant women or passive immunization at birth. I think that's the way it has to be done right now. And if we can start doing that, I think that that'll really make a big difference in terms of hospitalizations for infants. It's been a great discussion, but I think we really-- The time is now where we really need to start protecting these infants

because the morbidity is huge. The possible benefit of this is huge also, and so it's time to move forward. Thank you.

Dr. El Sahly: Great. Thank you. Dr. Kotloff?

Dr. Kotloff: Sure. So, I think that it's a very good idea for the reasons that we said that you get early protection, that these look very, very effective. The data on nirsevimab in the second half of infancy, there were fewer cases, so it was less clear, but I suspect that there may be longer immunity. I agree that we need to watch carefully for immune escape, but even with vaccines as we know well from COVID, you can have immune escape. So, that's a universal problem. I also think that when we're talking about intranasal vaccines, I don't know the data on developing countries, but the universal purulent rhinitis, I don't know whether that's a consideration as well. So, I think that all live-attenuated vaccine constructs or parenteral constructs on all populations are not the same. And we have to be clear about our approach when we're solving these problems for different populations. So, in terms of the data on whether there was muting of the antibody responses, I think that, from what I remember of the graphs, they went by quickly, but I think that the kids who had gotten monoclonal antibodies had very, very high antibody levels. So, it's much more difficult to see a fourfold rise when you're starting with such high antibodies. That doesn't mean those kids aren't protected. So, I think for that, we need to understand the kinetics better. And for all of this, we need to do studies to answer these questions.

Dr. El Sahly: I have the table pool. They started with 10,000 and ended with 7,000. It's like flat completely, but yeah. Dr. Nelson?

Dr. Nelson: Yeah. Thank you. I agree with my colleagues, certainly not enough as evidence to raise concern over our current approach and use of nirsevimab, and

certainly would recommend continuing our current approach. I would state that going forward, it is going to be difficult to discern a true humoral response. Our humoral immune status and immune response is always going to be a mess with a mix of vaccine response, maternal contributions, natural infections, and now passive monoclonals. So, I would put more emphasis and more resources and effort into the characterization of the cellular immune response and other better correlates of protection, and recognizing that we're dealing with small infants, we're going to have to take advantage of new technology with small samples using transcriptomics, multiplex approaches, and even selective cell activation status using high-dimensional flow cytometry. Could be certain methodologies that could be selectively employed in these trials. Thank you.

Dr. El Sahly: Thank you. Dr. Offit?

Dr. Offit: Yeah, I'm not sure I have anything much to add. I agree with my previous Committee members here who have spoken. We're being asked to make a decision on still relatively small numbers. I think this is obviously an issue of efficacy, not safety. And so as Dr. Monto said, let's keep our eyes open, continue to do studies, gather more data, and then I think we'll be able to speak on this in a more informed manner. Thank you.

Dr. El Sahly: Thank you. Dr. Janssen.

Dr. Janssen: Yeah, just to follow in what Dr. Offit said, I'd just like to see more data, more of the same data would be helpful.

Dr. El Sahly: Thank you. Dr. Meyer?

CAPT Meyer: There I go. All right. So just to echo my other Committee members, I think the data presented there were too few-- It is too small of numbers to really go on. I

think just one comment to echo. I think it was Dr. Gans who said-- I mean, I think we really have to think through the clinical significance. Even if we did find blunting, we've seen this before with some other vaccines like maternal pertussis where we do see some blunting. We don't really know if that's clinically significant, but it is overcome by getting boosters. So, I think any data we do collect on blunting of the immune response, we just have to look at some of those other things too, like if it is actually clinically significant or not.

Dr. El Sahly: Thank you, Dr. Perlman.

Dr. Perlman: Yeah, I think most of what I was thinking has been said. I also think it's a possibility that there's going to be an effect, but whether it matters or not, we have to just figure it out by getting more data. And the second part, whether the antibodies would have an effect on all vaccines, I wonder if we use a protein vaccine or something else, if we ever have any risk of antigen antibody complex formation by having the right ratio of antibody and antigen. But again, it's something that could be easily thought about and measured when the time comes.

Dr. El Sahly: Thank you. I think everyone got an opportunity to weigh in on this question of Topic 1. Did I miss anyone? Okay. So to summarize Question number 2, the observed blunting in this particular clinical trial was observed in obviously a small sample size, 9 versus 6, and the timing from nirsevimab is 8 to 12 months. The comment-- In addition to it being a small sample size, it remains unclear what duration of protection nirsevimab will afford. And because that also has implications for future clinical trials, what time variable will be used to administer those vaccines. This occurred with one platform, how these findings translate to other platforms, of course, it's unknown. So, this will have to be assessed platform by platform. And as more data

comes along, this can be further discussed. Its effect on vaccine safety and effectiveness obviously cannot be gleaned from these data as presented. And however, from earlier in the day, we did point out that the individuals in this particular arm of the study need to be carefully followed through the upcoming RSV season to see if there's any particular immunologic finding that could be of interest to the development of these vaccines. Did I miss a particular point on this question? Okay. Well, we finished two minutes earlier, but thank you all for weighing in with your expertise on this particular topic as little or as much data we have on hand. I have a final question to the FDA before we adjourn this particular-- Or actually, two questions. First, did we answer and discuss the two discussion questions okay? Or are there particular items that we need to address?

Dr. Kaslow: No. So, thank you very much for your deliberations. We'll certainly take back to our internal discussions, your discussions and recommendations, and the goal of which is to have a timely engagement with sponsors of pediatric RSV vaccines. So, thank you very much. I would say mission accomplished.

Dr. El Sahly: Well, the second question, there's a lot that seems to be at play now in terms of immunologic assays, data from CDC, data from sponsors, data from FDA. Again, I guess I don't know, would the follow-up meeting from a year from now be of use or maybe not? I don't know. Maybe my curiosity is acting here, but--

Dr. Kaslow: There is a lot to synthesize. There's a lot to better understand. There are data that are still coming in. I don't think any of us want to stall development of vaccines, the unmet medical needs. And so like today, getting your input is incredibly helpful. As we look going forward in this area, more data, better understanding, there's a likelihood we'll be back to see you again.

Topic I Adjournment

Dr. El Sahly: Alright, very good. Thank you. And at this point, I want to thank four temporary members with us today, Dr. Long, Dr. Malloy, Dr. Kotloff, and Dr. Ruckwardt. So, that concludes your participation on today's meeting. Thank you so much for the time and expertise you lent today. And for the rest of the team, we take a 10-minute break. So that puts us at 3:10.

Topic II

Opening Remarks: Call to Order and Welcome

Dr. El Sahly: Good afternoon, everyone. I would like to welcome the members, participants, and the public who are viewing remotely to the 188th VRBPAC meeting. This is Topic II, open session. I would like to turn over the meeting now to Dr. Sussan Paydar, the designated federal officer who will proceed with administrative issues.

Roll Call

Dr. Paydar: Great. Thank you, Dr. El Sahly. Good afternoon, everyone. For those who didn't attend the morning session, we have completed Topic I and we are about to begin Topic II to hear overviews of the Laboratory of Immunoregulation (LI) and Laboratory of Retroviruses (LR) research programs in the Division of Viral Products, Office of Vaccines Research and Review, Center for Biologics Evaluation and Research. Next slide please. AV Team? Next slide, please. Great.

Once again, I would like to thank CBER Senior Leadership, Dr. Marks, Dr. Kaslow, Dr. Bok, and Dr. Agnihothram. Next slide, please. I would also like to thank Senior Leadership that were closely involved in topic II. Dr. Karen Elkins, Associate

Director for Science, Office of the Director, CBER; Dr. Todd Merkel, Associate Director for Research, Office of Vaccines Research and Review; and Dr. Jerry Weir, Director, Division of Viral Products, Office of Vaccines Research and Review. Next slide please.

The attending members for Topic II are Dr. Hana El Sahly, the Chair; Dr. Adam Berger; Dr. Henry Bernstein; Dr. Archana Chatterjee; Dr. Hayley Gans; Dr. Holly Janes; Dr. Robert Janssen, our alternate industry representative who will be attending only the open portion of this topic; Captain Sarah Meyer; Dr. Arnold Monto; Dr. Michael Nelson; Dr. Paul Offit; Dr. Stanley Perlman; Dr. Jay Portnoy, our consumer representative; and Dr. Andrea Shane. We have a total of 14 participants, 13 voting and 1 non-voting member.

Conflict of Interest Statement

Now, I'll proceed with reading the FDA Conflicts of Interest Disclosure Statement for the public record.

The Food and Drug Administration (FDA) is convening virtually today, December 12th, 2024 for The 188th Meeting of the Vaccines and Related Biological Products Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. Under Topic II, the Committee will hear an overview of the research programs in the Laboratory of Immunoregulation (LI) and Laboratory of Retroviruses (LR) in the Division of Viral Products, Office of Vaccines Research and Review, CBER. Per agency guidance, this session is determined to be a non-particular matter, which would have no impact on outside financial interests. Hence, for Topic II, no external affected firms or entities were identified, and members were not screened for this topic. After the open session is completed, the meeting will be closed to permit

discussions where disclosure would constitute a clearly unwarranted invasion of personal privacy 5 U.S.C. 552b(c)(6).

This concludes my reading of the Conflict of Interest Statement for the public record. At this time, I would like to hand over the meeting to our Chair, Dr. El Sahly. Dr. El Sahly?

Overview of Research/Site Visit Process, CBER

Dr. El Sahly: Thank you, Sussan. To kick us off, Dr. Karen Elkins from the FDA will be giving us an Overview of Research and Site Visit process at CBER. Dr. Elkins is the Associate Director of Science at the Office of the Director, CBER, FDA.

Dr. Elkins: Thank you very much, Dr. El Sahly. Yes, I'd like to give you just a short overview of CBER's Research Program and how it relates to our regulatory responsibilities just to give you some context for your consideration of today's Site Visit Report. Next slide, please.

As this Committee well knows, CBER is responsible for regulation of biological products and specifically vaccines, in this case. Next slide, please. And we have a rather unique approach to our regulatory responsibilities in that CBER's Research and Review are integrated, and our research staff conduct regulatory reviews, specifically chemistry, manufacturing and control product reviews, and I'll say a bit more about that in a second. And we've been doing business like this for a very long time, pretty much since the beginning of CBER over 75 years ago. We conduct investigator-initiated research that is directly related to the products that CBER regulates, and we are looking specifically for gaps in knowledge and gaps in tools that limit product development. And so the topic of our research may range from something that looks fairly basic, if

that's the major gap, to something that looks very targeted, if that's the major gap. One way or the other, our research studies inform regulatory decision-making and policy development. Next slide, please. And research is such an integral part of the way in which we operate, that it is one of four explicit goals that are part of CBER's strategic plan. Next slide, please.

We have robust laboratory facilities on the White Oak Campus in Silver Spring. We have about 450,000 square feet of space that houses about 150 laboratories ranging from BSL-1 to BSL-3 labs. We have about 65 PIs currently, and about 425 total research staff. We have some excellent research core facilities that provide common services like flow cytometry and molecular biology services, and we have a state-of-the-art vivarium. Our funding comes primarily from annual congressional appropriations. We also have some funding from targeted CBER funds and FDA-wide programs and a few external grants. And our staff is a mix of permanent principal investigators, permanent staff scientists who are subordinate to PIs, technicians and research fellows that are typically temporary. Next slide, please.

Our researchers function as part of regulatory review teams and typically their main assignment is CMC or product review. They're responsible for critiquing the scientific rationale for a particular product and any data that is submitted in support of proof of concept of that product. They're responsible for everything about the product, the way in which it is made, the techniques that are used for manufacturing and the facilities in which it is made, and for all aspects of product quality control testing, both in the intermediate and final lot release test. Most clinical trials have clinical samples obtained from patients that are assessed in laboratory settings, and our researcher reviewers are also responsible for critiquing the clinical assays that assess those samples. So, the CMC reviewers function as part of a larger team typically comprised of

a regulatory project manager who manages the file and provides oversight, a clinical reviewer who focuses on clinical trial design and monitors the progress of the trial itself, a pharma and tox reviewer who focuses on those aspects, and a statistical reviewer who helps with analysis of data but coming from both the product side and the clinical trial itself. Next slide, please.

So, we think that operating this way has a number of advantages. It directly develops knowledge and tools that support development of classes of products. It also develops the hands-on, state-of-the-art understanding of the techniques that are the source of data that we see in our regulatory submissions. It facilitates recruitment and retention of highly trained scientists and it prepares us for the future review of innovative products and public health challenges, as we just lived through. Collectively, we think a Researcher-Reviewer model ensures efficient, effective and credible review and decisions that are based on sound science. Next slide, please.

So, we evaluate our research continually in a number of approaches. Projects are reviewed annually by direct supervisors and all layers above them. New projects come under specific scrutiny by the Office and the Center. We have Horizon Scanning efforts both at the Office level and at the Central level, and the results of those feed into the topics under consideration for the research portfolio. And we have a process known as the Site Visit that is the subject of today's discussions. This is a periodic review by an external Committee of subject matter experts that should take place every four years. We've had some deviation from that schedule thanks to the pandemic, and there have been longer gaps between site visits as you'll see today. Next slide, please.

The evaluation criteria will be familiar to most people. We expect our science to be excellent. We expect it to be widely disseminated in the form of publications,

presentations, occasionally technology transfer, impact on guidance documents, and one way or the other to have excellent uptake by the scientific community and impact for our regulated stakeholders. And we expect it to be relevant to our mission, to align with our goal, and to support product development and to provide review capability. Next slide, please.

Within CBER, we have eight offices. Currently, three of those conduct laboratory-based research. The offices are divided into divisions, and divisions divided into units that are called either labs or branches, those terms are interchangeable. And the site visit process is at the level of a lab. And there are two labs that will be under discussion today. For site visits, PIs provide written reports about their progress and plans. Those are received by the Review Committee who convenes for one to two days of presentations, oral presentations, discussion and questions about the presentations and the material report itself, and individual interviews with PIs. And also during the site visit itself, reviewers confer to critique the strengths and weaknesses of each PI's program with a view toward generating a report of their findings. Next slide, please.

We ask reviewers to comment on the quality and relevance of the science, its progress and productivity since the last site visit in the context of the work's nature, its resources and regulatory assignments to the individuals involved. The review is primarily retrospective, but we also ask for comment on the future research direction and any comments on the lab organization, its management and mentoring are also welcome. Next slide, please.

The site visit culminates in a report that's generated by the Review Committee. It is a draft report until it is presented to you, and that is our activity today. There are three possible outcomes of the presentation of the report. You may choose to accept it

and approve it as is, you may choose to amend the report yourself and then consider it for approval, or you may choose to reject the report and send it back to the original Site Visit Committee for further consideration. Two of the members of the VRBPAC served as Chair and Co-chair of the Site Visit Team itself, which was then comprised of ad-hoc reviewers, and so I'm sure they will be available to answer questions about the event itself. When you vote on it, it is then finalized upon your approval. The final report is used in many ways. Obviously the feedback goes to the PIs and their staff, and used to improve the progress of their research. It's used internally to review individual scientists' progress, and it's used throughout the center to consider program adjustments, resource allocation, and consider the nature of the work in the context of the overall CBER Research Portfolio. Next slide, please.

So with that, I'd like to thank you very much for your deliberations. Site visits are a really important part of our research activities. They really help maintain high-quality research programs. This external review really is critical to fulfilling our regulatory mission, and I'm happy to answer any questions that you might have. Thank you very much.

Overview of Research/Site Visit Process, CBER – Q&A

Dr. El Sahly: Thank you so much, Dr. Elkins. I invite the Committee members to use the raise-your-hand function if you have questions for Dr. Elkins. I know we did a couple of those in the last three months, so maybe you explained the process clearly to them.

Dr. Elkins: Thank you. And my colleagues will drill down further for information directly related to the labs under review today.

Dr. El Sahly: Great. Thank you for your time, Dr. Elkins.

Dr. Elkins: Thank you all.

Overview of Research Conducted in Office of Vaccine Research and Review, CBER and Division of Viral Products

Dr. El Sahly: I'd like to invite now Dr. Merkel. Dr. Tod Merkel is the Associate Director of Research, Office of Vaccine Research and Review. He will give us an Overview of Research conducted in Office of Vaccine Research and Review, CEBER and Division of Viral Products.

Dr. Merkel: Alright, thank you. Could I have the next slide, please? So, the Office of Vaccine's mission is to protect and enhance the public health by assuring the availability of safe and effective vaccines, allergenic extracts, and other related products. We regulate vaccines, allergenic products, live biotherapeutic products, and phage. Next slide.

Our core activities are to review, evaluate, and to take appropriate action on INDs, BLAs, amendments and supplements for vaccines and related biological products. And we also participate in the inspection of manufacturing facilities. We develop policies and procedures governing the pre-market review of regulated products. And as you've heard, we conduct research related to the development, manufacture, and evaluation of vaccines and related products, and also research to better understand the pathological processes of the agents that the vaccines are directed against. Next slide.

The OVRR's Research Program is designed to complement and support our regulatory mission by focusing on issues related to the development of safe and effective products. Next slide. The Research Program contributes to our regulatory

efforts in really important ways. We have a very strong emphasis on safety in OVRR because our products are often designed for mass use, often universal use. Many of our products go into every child that's born in the United States, and our recipients are healthy individuals. And as I said, often children, hence our emphasis on safety.

Our products, vaccines in particular, undergo a high level of scrutiny by the public, both groups that are skeptical of vaccine effectiveness and groups that are anxious to have new vaccines brought to market as quickly as possible. And because of this high level of scrutiny, our regulatory decisions have to be based on excellent science. We also need to keep pace with technology. New manufacturing technologies are rapidly evolving and coming online and new and powerful research approaches are constantly being developed, and it's important for us to keep our finger on those advances. We need to be flexible and respond rapidly to public health threats. We have a continuing evolution of antibiotic resistance and concerns about emerging agents.

As Dr. Elkins pointed out, our ability to respond rapidly to the COVID-19 pandemic, I think largely grew out of our excellent research program. Generating-- The results we generate are placed in the public domain. So, our research benefits not just an individual company but the entire industrial sector, and therefore American consumers. And our research program allows us to recruit and retain expert scientists to support our regulatory review. Next slide.

Our Research Program is very broad, although we can't cover everything, we do try to cover as much as possible within the scope of our responsibilities. It's very collaborative. Our scientists collaborate to a very large extent, both internally but also externally with scientists around the country and around the world, and this allows us to leverage our investments in research. Our research is excellent. It is published and

broadly cited and used. And our research scientists, importantly, are members of the broader scientific community and many are well-known experts in their fields. And our research is investigator-initiated and flexible. And this is important because it allows our researchers to anticipate regulatory needs and redirect their research program to address those needs when necessary. Next slide.

The OVRR is made of-- In addition to the Office of the Director, it has four divisions. Two of those divisions, the Division of Review Management and Regulatory Review and the Division of Clinical and Toxicology Review are focused primarily on regulatory review of files. Our two Research Divisions, the Division of Viral Products and the Division of Bacterial Parasitic and Allergenic Products, in addition to conducting regulatory review, conduct research. And the subject of today's activity is the review of two laboratories within the division of Viral Products, which is directed by Dr. Jerry Weir and Deputy Director Robin Levis. Next slide.

DVP's mission is to regulate viral vaccines and related biological products to ensure their safety and efficacy for human use, and to facilitate the development, evaluation and licensure of new viral vaccines that positively impact the public health. Next slide. Their major responsibilities are the review of Investigational New Drugs applications, Biological License Applications, and other pre-marketing activities focused on viral vaccines. Review of BLA supplements, lot release, and other post-marketing activities. The inspection of manufacturing facilities, both pre and post-licensure. Consultation with other public health agencies, for example, the WHO, the CDC and NIBSC. And to conduct research related to the development, manufacturing, evaluation, and testing of viral vaccines. Next slide.

The role of the research program in DVP is to research and laboratory activities that complement the regulatory mission. They address issues related to regulated viral vaccines and they anticipate and address issues related to the development and evaluation of new viral vaccine products, both general issues that are applicable to many products, for example, cell substrate issues or improved testing methods, as well as specific product issues. For example, developing correlates of protection and animal models. Next slide.

The Division of Viral Products is directed by Dr. Jerry Weir and Deputy Director Robin Levis. It consists of seven laboratories. The two laboratories that are subject of today's meeting are the Laboratory of Retroviruses and the Laboratory of Immunoregulation. Next slide. I'd just like to thank you and take any questions.

Overview of Research Conducted in Office of Vaccine Research and Review, CBER and Division of Viral Products – Q&A

Dr. El Sahly: Thank you Dr. Merkel. Any questions from the Committee members? Okay, I don't see any raised hands. Oh, we do. Dr. Perlman?

Dr. Perlman: Yeah, so this is not quite relevant for what we're doing today, but these laboratories have really overlapping laboratories within them. So, the names are not so applicable anymore, in my opinion. If you agree, is there any chance of renaming them so they're more consistent with what they do?

Dr. Merkel: Yes. I mean, the reality is that over time, what they do changes and the names don't, which is where this comes from. Changing the laboratory name isn't as simple as just changing the name. I mean, there are underlying protocols that would

have to be followed, but at this time we're in the process of renaming several of the laboratories, so we have noted this comment in the past.

Dr. El Sahly: Great. Dr. Perlman will share the Committee on naming. Any other questions? Hearing none. Thank you, Dr. Merkel.

Overview of Laboratory of Immunoregulation

Dr. El Sahly: I would like to invite now Dr. Weiss. Dr. Carol Weiss is Chief and Principal Investigator, Laboratory of Immunoregulation, Division of Viral Product at OVRR, CBER. Dr. Weiss will give an Overview of Laboratory of Immunoregulation. Dr. Weiss?

Dr. Weiss: Okay. Good afternoon, everyone. And I thank the Committee for their help in reviewing our Research Programs. Next slide, please. So, in this overview of the Lab of Immunoregulation, I will briefly mention the staff structure, our regulatory activities, the research programs at a very high level, and just highlight a few research results and their impact. So, next slide, please.

So, the Lab of Immunoregulation has two principal investigators, Dr. Ira Berkower and me. In my lab, I have one lab manager who is responsible for lab ordering budgets and general lab maintenance for both my lab and Dr. Berkower's lab, and as well he's an integral member of our research team. I also have two staff scientists or staff fellows who share responsibilities in both doing investigator-initiated research and regulation. And generally, I have one to two either post-baccalaureate or post-doctoral fellows that I get through awarded competitive grants. Dr. Berkower's lab has on average one to two post-baccalaureate or post-doctoral fellows.

In my Research Program, I also work with many lab collaborators and from many different institutions. So, for our COVID-19 response efforts, we have been very much involved with various HHS agencies including NIH, CDC, BARDA and ASPR. We've also had many collaborators in the Department of Defense and the Uniformed Services Universities where we've been helping with the investigations of the clinical trials and vaccine trials that have been undertaken by the Department of Defense for antigenic cartography studies. We also collaborate with investigators at NIAID. And as well, for very specific influenza and SARS-CoV-2 studies, we also collaborate with many of the PIs in our own division. Next slide, please.

So, as you've heard, our primary responsibilities are to provide expert scientific review of FDA submissions for both experimental and licensed vaccines for preventing viral infectious diseases. As our programs are lab-based and we are active researchers, our primary focus is really product review. That's the CMC review that you heard about where we focus on product quality, purity and potency as well as manufacturing process consistency. Dr. Berkower and I have also been involved with clinical review, which involves review of clinical protocol safety, immunogenicity, and efficacy data. And that has been focused primarily on experimental HIV vaccines for treatment and cure strategies that often involve complex trial designs with antiretroviral treatment interruptions. Next slide.

So, our regulatory activities involve primarily the review of the submissions, and this includes all types of files and their associated meetings with the sponsors. So, this is PreINDs, INDs, Master Files, BLAs and BLA supplements for post-approval manufacturing changes. So, once a vaccine is on the market, there are very frequent manufacturing changes and we need to look at the comparability studies to make sure there's effect on the product. We've also been involved with inter-center consults. Our

review portfolio includes experimental vaccines for HIV, influenza, and coronavirus, and approved vaccines for influenza and papilloma virus. We've also been involved with advisory meeting preparations. This has included discussions with vaccine stakeholders. We have directly contributed data for some of these discussions as well as contributed data and efforts in preparing briefing materials for the Advisory Committee meetings. Next slide.

We've also been involved in other public health activities that bear on the regulation. So, for the COVID-19 response efforts in particular, my team was very much involved with the Operation Warp Speed, Therapeutics Research Team. We've also been involved with the HHS Interagency Working Groups where we've contributed data, presentations, and risk assessments. This has been working groups that involve COVID-19 testing, assays, therapeutics, and vaccines. Also, the NIH SARS-CoV-2 variant evolution program for responding to the latest SARS-CoV-2 variants. And I've also been involved in a couple risk assessments that have involved the use of therapeutic COVID-19 antibodies, as well as a reevaluation of the biosafety level for use of live SARS-CoV-2. I also-- My team also participates in regular working group meetings with our collaborators over the Department of Defense and the Uniformed Services University. In addition, some of our work has involved international work on international biological standards and regulatory harmonization efforts. So, this has included WHO International Standard for anti-SARS-CoV-2 immunoglobulin and a reference panel for SARS-CoV-2 variants of concern. We've also been involved in many inter-laboratory SARS-CoV-2 assay comparison studies involving several different consortia including Duke, NIH and the Uniformed Services University. We've also participated in the FLUCOP study, which was a cross laboratory comparison of

hemagglutinin nation inhibition and microneutralization assay performance for seasonal influenza vaccines. Next slide.

So, really our laboratory expertise informs all components of the product review. And so, especially as virologists, it's important for viral vaccines, so we review all manufacturing process steps to assure product safety and consistency. As examples, we look at virus growth steps, purification steps, ensure that the methods that are used are valid. We're interested in methods for detecting adventitious agents as well as product comparability studies when there's been manufacturing changes. We review, also as an example, important steps in viral inactivation to assure product safety. So, we look very carefully at the inactivation procedures for inactivated vaccines and also for adventitious agents. And then as a corollary, also the methods for detecting residual infectious virus to ensure that it's appropriate and sensitive. We review assessments of replicating vector stability and antigenicity to ensure safety and potency. We review potency assays to assure product lot-to-lot consistency and potency, and finally review and participate in assessments of immunogenicity measurements and assays that actually directly support licensure. Next slide, please.

So, the Laboratory of Immunoregulation has two research programs run by each PI and these are independent research programs. So in my program, the overall theme is both basic and applied studies of virus entry into cells and its neutralization by antibodies. So, since the last site visit, we were finishing up before the pandemic some influenza studies that included antibody correlates of protection during an H3N2 influenza outbreak in military recruits. We also compared antibody responses elicited by the different approved seasonal vaccines that are manufactured using eggs, cells, or recombinant protein methods. And we also generated a novel antibody targeting a conserved stem region of the influenza hemagglutinin and characterize its escape. But

most of the time since the last site visit really has been spent on SARS-CoV-2 studies and our focus had been variant characterization and immune escape as well as mutations that confer resistance to therapeutic antibodies as well as post vaccination sera. Dr. Berkower's lab program focuses on live-attenuated rubella vector for antigen delivery and protection, as well as vector prime boost vaccine strategies focused on HIV protection and cure. Dr. Berkower's program was not reviewed in this site visit cycle, so I will not be mentioning it further. Next slide.

So, here I'm just pulling out just a few selected highlights of our studies in this past cycle. So, for the influenza studies, we looked at the 2018-2019 seasonal influenza vaccines and found that both the egg and the cell-based vaccines elicited very similar neutralization titers against all of the vaccine viruses, and that the titers elicited by the recombinant HA vaccine were actually slightly higher against all these viruses as well. For the SARS-CoV-2 studies, based on our prior very basic research on HIV as well as influenza, we were able to quickly establish a safe pseudovirus neutralization assay for characterizing SARS-CoV-2 variants and measuring antibody neutralization. We also identified mutations that confer resistance to therapeutic antibodies and post-vaccination sera. We also showed that primary mRNA COVID-19 vaccination series elicited broader and higher neutralization responses against the variants than infection alone by a single variant. And we also characterized antigenic changes in variants that inform decisions about the variant composition update to COVID-19 vaccines. Next slide please.

So, I just from a high level emphasize the overall research contributions that really cover many different aspects. So, firstly and importantly, they provided laboratory expertise for supporting scientific regulatory review. As I mentioned, the assessments of all the manufacturing processes and testing methods. It also gives us

credibility and important contributions in our technical communications with the vaccine developers. And as well, as shown by our SARS-CoV-2 studies, having broad-based current research methods gives us agility for adapting to changing priorities for the Center. We've also generated materials and methods for actually facilitating the development of vaccines. We developed some new cell lines, and one of them was supported high level transduction of SARS-CoV-2 pseudoviruses which have been shared widely in the scientific community and are available in a repository. We helped develop assays and harmonized assays, as well as reference materials as I mentioned, as well looking-- Participating importantly in these multi-laboratory harmonization methods of methods that are used for vaccine evaluation. And finally, we have contributed data directly for the science-based regulation. The data has been used in both internal discussions and with meetings with vaccine stakeholders, and also have been widely disseminated in peer-reviewed scientific journals for the broader community. And with that, I'm over. I've finished my talk and I'm happy to take questions. Thank you.

Overview of Laboratory of Immunoregulation – Q&A

Dr. El Sahly: Great. Thank you so much, Dr. Weiss. Any questions from the Committee members? That was a whirlwind of a lot of work. Use the raise-your-hand function should you have any questions. Okay. I guess no questions today. Thank you so much, Dr. Weiss.

Dr. Weiss: Thank you.

Overview of Laboratory of Retroviruses

Dr. El Sahly: Know we asked a lot of questions during our meeting a couple of months ago. I'd like to invite now Dr. Golding. Dr. Golding, Hana Golding, is Chief and Principal Investigator, Laboratory of Retroviruses in the Division of Viral Products, Office of Vaccines Research and Review. Dr. Golding will give an Overview of Laboratory of Retroviruses. Dr. Golding?

Dr. Golding: Thank you very much and I want to thank again both the side visit team and the current members of the VRBPAC for their input to our research program. Next slide, please.

So, we have two units in the Laboratory of Retroviruses, the Unit of Viral Immunology and Pathogenesis, and the overall title of the program is Development of New Immunological Assays and Animal Models Evaluate Vaccine Safety and Efficacy. In addition to myself as the PI and the Lab Chief, I have two senior staff scientists at the high level, Marina Zaitseva and Surender Khurana that carry on both the mentoring of the independent project as well as regulatory work. And we are assisted by Jody Manischewitz, Lisa King and David Acosta, and we, during the years, have mentored between five to six post-doc, post-bacc, and contracts per year. Next slide.

The unit headed by Arifa Khan is the Unit of Molecular Retrovirology and the emphasis of the project is Development of Sensitive Virus Detection Assays for Safety of Vaccines and Other Biologics and Evaluation of their Potential Threat for Human Infection. In addition to Dr. Khan, the lab includes several staff scientists and staff fellows. Hailun Ma, Andrea Kennard, Sandra Fuentes, and Pei-Ju Chin, and they have always mentored between two to four post-doc, post-bacc, and contracts. Next slide, please.

I like to always introduce our program, similar to what Dr. Merkel mentioned, and that's a famous slide by Dr. Fauci that keeps reminding us the arena, and that there are constantly newly emerging diseases and it's sort of a moving target. All of those in red are newly emerging, while the blue are emerging, and in the last four or five years we had to deal with many of these, including of course, coronavirus, monkeypox, and the reemerging H5N1. Next, please.

And as Dr. Merkel mentioned, the goal of our program is to identify regulatory and scientific gaps in knowledge methods for vaccine release and correlates of protection. LR researcher-regulators provide CMC expertise and readiness to redirect their scientific programs to meet the challenges of the emerging diseases, including the use of new cell substrates, manufacturing platforms, novel immunogen and adjuvant design, and clinical protocols. How do we do it? By developing advanced technologies for improved analysis of known and emerging viruses for evaluation of cell substrate and product safety, humoral immune responses post-infection, immune response to novel viral vaccines, adjuvant safety and mode of action, vaccine potency assays, and animal models for preclinical evaluation of vaccines including safety and effectiveness. Next slide, please.

The type of regulatory work is actually-- Our regulatory portfolio is extremely diverse. It includes vaccines against the following human pathogens: HIV, influenza, RSV, SARS-CoV-2, and many, many adjuvanted vaccines across both the Division of Viral Product and our sister, DPEP, as well as across the multiple centers. The platforms that we are looking at are as diverse as the viruses. They include non replicating and replicating viral vectors, Poxviruses, NDV, PIV, DNA vaccines, mRNA vaccines, live-attenuated vaccines, recombinant proteins, peptide-based vaccines and nanoparticles. Novel adjuvants are one of the large responsibilities of LR, as well as a vaccine delivery

system and routes, universal influenza vaccines, and novel cell substrates and detection of adventitious agents using next generation sequencing technology, which is led by Dr. Khan, that include mammalian tumorogenic and non tumorogenic cell lines, insect cell lines for baculovirus expression vectors, and avian cell lines. Next slide, please.

The regulatory work that's kind of detailed here has increased significantly since the last site visit, and if you look in the right for both labs, the increase in the numbers of original IND amendment and pre-IND including BLA, increased between 150% to 250%. Next slide.

In addition to the direct regulatory work, we members of LR have been involved in guidance documents. Dr. Khan, particularly in ICH, WHO, EDQM and USP guidelines on the implementation of NGS technologies for enhancing safety of vaccines and cell substrate. We are involved with WHO guidelines on nonclinical safety evaluation of vaccine adjuvants and adjuvanted preventive vaccines for infectious disease indications, and FDA guidance for industry on pharmacogenomic data submissions. There were multiple WHO consultations and BARDA presentations as well as cross-office and cross-center consults. Next slide, please.

So, the scientific project in my lab was quite diverse and very much reflected our response to emerging and reemerging diseases. Elucidation of humoral immune response following Ebola and Marburg infection and vaccination was led by Dr. Khurana; SARS-CoV-2 pathogenesis; antibody responses following SARS-CoV-2 infections versus vaccination in different cohorts that included adults, pediatrics, including MISC as well as immunocompromised individuals; elucidation of humoral immune responses following RSV infection and vaccination in different age groups; influenza vaccines, seasonal, pandemic and next generation/universal vaccines; mucosal

vaccines; and adjuvant safety that included in vitro human cell-based assays for testing of novel adjuvants including primary monocytes, differentiated macrophages, and broncho-epithelial cells grown under Liquid-Air-Interface that was led by Dr. Zaitseva. Next slide.

I just wanted to outline some of the methods that have to be implemented to respond to all these pathogens. First of course, virus neutralization assays for influenza. We looked both at hemagglutination inhibition and microneutralization assays using all available vaccine strains using the CDC protocol, and we were part of the FLUCOP and the [Indiscernible 00:47:30] to demonstrate the added value of standards for some of these assays. RSV (A/B), we developed an RSV luciferase reporter-based neutralization assay in addition to PRNT. And for SARS-CoV-2, similar to Dr. Weiss, we are using the lentivirus based pseudovirus neutralization assay against all circulating strains and variants of concern. Next slide.

One of the important technologies that was introduced by Dr. Khurana in the lab is the generation of whole-genome phage display libraries. This technique basically subjects the genome to limited DNA's digestion that generates both large and smaller fragments. The larger fragments are expected to express some important conformational epitopes and after polishing, it's been cloned as a fusion protein with the extracellular gIII fusion protein of phage. And after electroporation, we are generating a very large library of phages, each expressing a unique epitope on this extra cellular. Next slide, please.

These kinds of phage display libraries have been generated chronically during the years against avian influenza, seasonal influenza, filovirus including Ebola and Marburg, Zika, and most recently the SARS-CoV-2. This type of technology really gave

us an opportunity to look at the unique repertoire of different polyclonal antibodies in multiple infections as well as post-vaccination. And what was interesting in the case of COVID, most recently, we were able to demonstrate the independent evolution of mucosal IGM, IGG and IGA repertoire compared with serum in asymptomatic versus symptomatic patients. In particular, we noticed that a significantly higher number of phages were bound by mucosal IGA in asymptomatic versus symptomatic patients. Dr. Khurana also looked at the repertoire of young children at pediatrics that were infected with COVID-19, either moderate cases or severe cases, as well as MIC, and found a significant number of differences between the repertoire of these different subpopulations, suggesting that you can really learn a lot by don't just looking at one particular region, but asking the virus and the sera to tell us what else is recognized. And that may even lead to identifying protective epitopes as well as diagnostic epitopes. Also, in the RSV field, we looked earlier at very young children right after their first infection versus older children and adults, and noticed significant differences in the repertoire during the aging. Next slide.

Another very important, I think, contribution of Dr. Khurana was the use of kinetics-- The ability to use biocore to measure real-time kinetics of antibodies affinity, and that has been demonstrated here by looking at the red and the blue curves. You basically look at the same post-vaccination sera with tenfold difference. The important thing to notice is that the on rates are affected indeed by the total antibodies as well as the maximum binding, but the dissociation is parallel between the two curves, suggesting that the dissociation rate is mainly reflecting of the overall or average avidity of the antibodies. And using the heterogenous sample model software, we are able to measure the average avidity of the antibodies.

Of course, this technology requires a very careful use of only-- Properly for the proteins that are on a chip density that allow single binding to each protein. We were able to use this technology to measure total antibody binding, isotype distribution, and antibody off-rates and avidity. And again, during the years, we were able to show that measuring affinity of antibodies either post-infection or post-vaccination can provide a very important additional insight in trying to understand symptomatic versus asymptomatic infections. For example, in the case of COVID, following the added value of adjuvants to vaccines, we were able to show that the adjuvanted vaccines with oil and water adjuvants not only led to epitope spreading, but also to significant increase in a affinity maturation which correlated directly with the breadth of cross neutralization. Similar types of studies were recently done following COVID vaccination, either alone or together with infection, and the increase in avidity was the main correlate with a broader cross neutralization of variants of concern, including some variants that happened later.

So, I would like, with that now, to move to Dr. Khan's program. Next slide. Evaluation of high-throughput/next-generation sequencing as technologies for adventitious virus detection in biologics. Generating reference materials for validation of high-throughput sequencing. Development of WHO virus standards for viromics; development of virus-infected cell standards for genomics and transcriptomics; and refinement and annotation of the Reference Virus Database. Determining the sensitivity and breadth of virus detection by short-read and long-read HTS technologies. Investigating adventitious agents and endogenous viruses for safety of cell lines used for manufacturing of biologics, including Sf9 insect cells used for baculovirus-expressed products and Chinese hamster ovary cells used for recombinant protein production. In vitro cell cultures and in vivo animal models to assess potential outcomes

of simian foamy virus infections in humans that involve characterization of SFV expression in infected human A549 cell clone; identification of SFV microRNAs as potential biomarkers or virus infection; in vitro studies of SFV replication and genome analysis to elucidate factors influencing virus expression. Next slide.

Some of the most outcomes of Dr. Khan's program. First of all, the development of reference viruses for HTS implementation. That included creation of CBER NGS Virus Reagents to support NGS development and advancement, and the first WHO International Reference Panel for Adventitious Agent Detection in Biological Products for NGS qualification and validation studies. Thus, reference reagents are publicly available for distribution free of charge. Secondly, providing a Reference Virus Database or RVDB for detection of known, emerging and novel viruses by HTS with the high diversity of viral sequences for broad virus detection, with reduced nonspecific cellular hits resulting in less computational time and reducing cost of unnecessary follow-up work to verify a true virus signal. This is also freely available. Next slide.

Generation of in-house data and by external collaborations to fill knowledge gaps for using HTS as a routine assay that included developing optimized protocols for analyzing HTS short-read and long-read platforms. Determining LOD for virus detection by HTS in different matrices relevant to biological materials during manufacturing for developing general regulatory and industry expectations. Developing virus-infected cell standards for HTS genomics and transcriptomics including all cell substrates, cell therapies, and unprocessed bulk harvests. Introduced HTS in international guidelines including ICH and new pharmaceutical European chapters to replace-- Very importantly, to replace the in vivo assays and PCR assays and to replace or supplement the in vitro cell culture assays. Dr. Khan organized international HTS trainings, webinars and workshops to facilitate establishment of HTS in Low-Medium

Income Countries and other regions considering use of HTS to replace the conventional assays for adventitious virus detection. Many of those trainings took place in 2024. With that, I will finish my presentation and both myself and Dr. Khan are available to answer any questions.

Overview of Laboratory of Retroviruses – Q&A

Dr. El Sahly: Wonderful. Thank you so much, Dr. Golding, for the presentation and importantly for all the work that this lab and Dr. Weiss's lab have been doing, preparing us for pandemics that happen and pandemics that did not happen. So, I invite the Committee members to use the raise-your-hand function to ask the investigators questions or comments, or anything they may have on the-- Okay, I don't see any raised hands functions. Thank you, Dr. Golding and Dr. Khan and the team. And we will be moving to the next session.

Dr. Golding: Thank you very much.

Open Public Hearing

Dr. El Sahly: Okay. Dr. Paydar, do we go to the OPH or does it have to be 25 minutes after the hour?

Dr. Paydar: No, we could go to OPH but there are no OPH-- So, you need to end. Yeah, we need to end--

Dr. El Sahly: Alright. So, the next item on the agenda is the Open Public Hearing Session. There were no Open Public Hearing Session requests. So, that ends the Open Public Hearing Session. I would like to hand the meeting over to-- First, I would like to

ask Dr. Janssen, who is the Industry Representative, to drop down. I want to thank you for being with us all day long for these important discussions.

Dr. Janssen: Yep. Thank you. Bye, everybody.

Transition to Closed Session

Dr. El Sahly: Thanks. And we hand the meeting over now to Dr. Marks and Dr. Kaslow before we move to the next session.

Dr. Kaslow: We'll wait to see if Dr. Marks has joined us. Oh, okay. So, as we go into the Closed Session, I'd like to thank VRBPAC for your service today. As always, your discussions and recommendations are critical input to our internal deliberations, especially when there's incomplete or just preliminary information to take a regulatory action. And Topic I today I think is an example of how VRBPAC discussions contribute to our deliberations. So, I'd like to thank all of today's temporary voting members, speakers for both Topic I and Topic II, as well as the FDA staff from OBRR and DSEC and our technical staff that ran yet another flawless virtual VRBPAC meeting. And a big thank you to you, Dr. El Sahly, for another beautifully chaired VRBPAC meeting. Back to you.

Dr. El Sahly: Thank you all. So, that ends the Open Session. We will now move to the Closed Session. So, I think now the electronic thing has to happen, right?

Dr. Paydar: No, I believe Dr. Marks just joined the call.

Dr. El Sahly: Yes, Dr. Marks.

Dr. Marks: I'm sorry. I was on and I dropped off for a moment. Sorry about that. I just wanted to echo what Dr. Kaslow said. I want to thank you very much. I think the discussion was really quite outstanding earlier today for Topic I and we appreciate all of

the work that goes into all of the laboratory evaluations and comments. So, I just want to say thank you so much for everything to the members. I think this Committee is incredibly important for helping to be transparent about what we do with the products that we regulate. This issue, I think, is important because there is a lot of complexity in the area of vaccines. But one thing I would just say so that anyone listening understands this, although there has been a very high-level discussion today of some very complex topics, the underlying principles of the products that are regulated, the soundness of vaccines and the principles of active immunization are unambiguous. So, really, I thank this Committee for the transparency that they help us provide to the public and for this scientific input to very complicated topics. I just really appreciate it and appreciate everyone. I think Dr. Kaslow already called out Sussan and all of the members, and you, Dr. El Sahly, thank you so much for everything. We also appreciate everyone who's tuned in today to listen to this, so I won't belabor things anymore. Thank you so much.

Dr. El Sahly: Thank you, Dr. Marks. So, I guess now we end the Open Session of the meeting and we will electronically move to the Closed Meeting, so no one logs off. Please, just stay where you are.