DEPARTMENT OF HEALTH AND HUMAN SERVICES

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FOOD AND DRUG ADMINISTRATION

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL PRODUCTS
ADVISORY COMMITTEE MEETING

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WEDNESDAY,
MAY 16, 2007

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The Committee met in Grand Ballroom of the Hilton Hotel, 620 Perry Parkway, Gaithersburg, Maryland, at 8:30 a.m., Ruth A. Karron, Chair, presiding.

COMMITTEE MEMBERS PRESENT:

RUTH A. KARRON, M.D., Chair (Not in Attendance for Topic I)
MONICA M. FARLEY, M.D.
PHILIP S. LaRUSSA, M.D.
STEVEN SELF, Ph.D.
BONNIE WORD, M.D. (Not in Attendance for Topic I)
JOHN MODLIN, M.D. (Acting Chair for Topic I)
SETH HERTHERINGTON, M.D. (Non-Voting Industry Representative)
LISA JACKON, M.D., M.P.H.
JACK STAPLETON, M.D.
HASSAN AZIZ, Ph.D. (Temporary Voting Member)
ROBERT DAUM, M.D. (Temporary Voting Member)
GAIL DEMMLER, M.D. (Temporary Voting Member)
BRUCE GELLIN, M.D., M.P.H. (Non-Voting Temporary Member)
RUTH HOFFMAN (Temporary Voting Member)
CAROLYN KERCSMAR (Temporary Voting Member)
PAMELA McINNES, D.D.S., M.Sc. (Temporary Voting Member)
LAWRENCE MOULTON, Ph.D. (Temporary Voting Member)
MELINDA WHARTON, M.D., M.P.H. (Temporary Voting Member)

EXECUTIVE SECRETARY PRESENT:

CHRISTINE WALSH, R.N.

I-N-D-E-X

P-R-O-C-E-E-D-I-N-G-S

8:31 a.m.

ACTING CHAIR MODLIN: On the record. I'd like to welcome you to the May 16, 2007 meeting of the Vaccines and Related Biological Products Advisory Committee. My name is John Modlin. I will be sitting in for Dr. Ruth Karron who has recused herself for this portion of the meeting. And to start with, I'll turn things over to Ms. Walsh for the usual administrative announcements.

MS. WALSH: Good morning. I'm Christine Walsh, the Executive Secretary for today's meeting of the Vaccines and Related Biological Products Advisory Committee. I would like to welcome all of you to this meeting of the Advisory Committee.

Today's session will consistent of presentations that are both open and closed to the public. Tomorrow's session will be open to the public. I would like to request

that everyone please check your cell phones and pagers to make sure they are off or in the silent mode.

I would now like to read into public record the Conflict of Interest Statement for today's meeting. The Food and Drug Administration (FDA) is convening today's meeting of the Vaccines and Related Biological Products Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the industry representative, all participants of the Committee are Special Government Employees (SGEs) or regular Federal employees from other agencies and are subject to the Federal Conflict of Interest laws and regulations.

The following information on the status of this advisory committee's compliance with Federal ethics and conflict of interest laws including, but not limited to, 18 U.S.C. 208 and 21 U.S.C. 355(n)(4) is

being provided to participants in today's meeting and to the public. FDA has determined that all members of this advisory committee are in compliance with Federal ethics and conflict of interest laws including, but not limited to, 18 U.S.C. 208 and 21 U.S.C. 355(n)(4). Under 18 U.S.C. 208, applicable to all Government agencies and 21 U.S.C. 355(n)(4), applicable to certain FDA committees, Congress has authorized FDA to grant waivers to Special Government Employees who have financial conflicts when it is determined that the agency's need for a particular individual's service(s) outweighs his or her potential financial conflict of interest (Section 208) and where participation is necessary to afford essential expertise (Section 355).

Members and participants of the Committee who are Special Government Employees at today's meeting including Special Government Employees appointed as

Temporary Voting Members have been screened for potential financial conflicts of interests of their own as well as those imputed to them including those of their employer, spouse or minor child related to Topic 1, Discussion and Recommendation on the Safety and Effectiveness of FluMist in a Pediatric Population Less Than 59 Months of Age sponsored by MedImmune; Topic 2, Overview of the Laboratory of Bacterial Polysaccharides and Laboratory of Enteric and Sexually Transmitted Diseases, Division of Bacterial, Parasitic and Allergenic Products, Office of the Vaccines Research and Review; Topic 3, Discussion and Recommendation of the Safety and Effectiveness of ACAM2000 Live Vaccinia Virus, Smallpox Vaccine, Percutaneous Scarification manufactured by Acambis Incorporated. Financial interests may include investments, consulting, expert witness testimony, grants, CRADAs, contracts, teaching, speaking, writing, patents and

royalties and primary employment.

Today's agenda involves a Discussion and Recommendation of the Safety and Effectiveness of FluMist in a Pediatric Population Less than 59 Months of Age. In accordance with 18 U.S.C. Section 208(b)(3), waivers were granted to Dr. Lisa Jackson, Dr. Carolyn Kercsmar, Dr. John Modlin and Dr. Lawrence Moulton. For Topic 3 related to the Discussion and Recommendation of the Safety and Effectiveness of ACAM2000 Live Vaccinia Virus, Smallpox Vaccine, Percutaneous Scarification, Dr. Lisa Jackson, Dr. Jack Stapleton and Dr. John Tearling received a waiver under 18 U.S.C. Section 208(b)(3).

Dr. Ruth Karron and Dr. Bonnie Word have recused themselves from the discussions related to Topic 1. Drs. Karron and Word may participate fully in the discussions of Topics 2 and 3. A copy of the written waiver may be obtained by submitting a written request to the Agency's Freedom of

Information Office, Room 12A-30 of the Parklawn Building.

With regard to FDA's guest speakers, the Agency has determined that the information provided is essential. The following information is made public to allow the audience to objectively evaluate any presentation and/or comments. Dr. Alexander Klimov is Chief Virus Surveillance and Diagnostic Branch, Influenza Division at that CDC. He will provide an update on the influenza strain selection.

For Topic 3, Dr. Gerald Parker is employed as the Deputy Assistant Secretary for Preparedness and Response, Department of Health and Human Services. Lt. Colonel Stephen Ford is Deputy Director of Scientific Affairs, Military Vaccine Agency, Office of the Surgeon General.

For Topic 3, Dr. Bruce Gellin, Dr. Michael Nelson, Dr. Lamone Collins and Dr. Gerald Parker are participating in this

meeting as Non-Voting Members. Dr. Seth Hetherington is serving as the Industry Representative acting on behalf of all related industry and is employed by Icagen Incorporated. In addition, Dr. Hertherington's spouse is employed by Glaxo SmithKline. Industry representatives are not Special Government Employees and do not vote.

In addition, there may be regulated industry and other outside organizations' speakers making presentation. These speakers may have financial interests associated with their employer and with other regulated firms. The FDA asks that in the interest of fairness that they address any current or previous financial involvement with comment upon. These individuals were not screened by the FDA for conflicts of interests. This conflict of interest statement will be available for review at the registration table.

We would like to remind members

and participants that if the discussions involve any other products or forums not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all other participants to advise the Committee of any financial relationships that you may have with the sponsor, its products and, if known, its competitors.

That ends the reading of the Conflict of Interest Statement. Dr. Modlin, I turn the meeting over to you.

ACTING CHAIR MODLIN: Thank you, Christine. I'd like to ask those who are seated at the table to introduce themselves and I think we'll begin with Dr. LaRussa.

DR. LaRUSSA: Philip LaRussa, Columbia University, New York.

DR. McINNES: Pamela McInnes,

National Institute of Dental and Craniofacial Research, NIH.

DR. DAUM: I'm Robert Daum, a Pediatric ID guy from the University of Chicago.

DR. FARLEY: Monica Farley, Infectious Diseases at Emery University in Atlanta.

DR. JACKSON: Lisa Jackson, Group Health Center for Health Studies.

DR. SELF: Steven Self, Biostatistics, Fred Hutchinson Cancer Research Center.

DR. WHARTON: Melinda Wharton, Center for Disease Control and Prevention, Atlanta, Georgia.

DR. MOULTON: Larry Moulton, International Health and Biostatistics at Johns Hopkins University.

DR. HETHERINGTON: Seth Hetherington, Icagen, Research Triangle Park, North Carolina.

DR. KERCSMAR: Carolyn Kercsmar, Pediatric Pulmonologist, Case Western Reserve University School of Medicine.

MS. HOFFMAN: Ruth Hoffman, Patient Rep., Director of Candlelighters Childhood Cancer Foundation.

DR. GELLIN: Bruce Gellin, National Vaccines Program Office, HHS.

DR. DEMMLER: Gail Demmler, Baylor College of Medicine in Houston and I do pediatric infectious diseases.

DR. AZIZ: Hassan Aziz, Professor of Medical Technology in Armstrong University in Savannah, Georgia.

DR. STAPLETON: Jack Stapleton, Infectious Diseases at the University of Iowa.

DR. BAYLOR: Norman Baylor at Food and Drug Administration, Center for Biologics Evaluation and Research.

DR. PRATT: Douglas Pratt, FDA CBER.

ACTING CHAIR MODLIN: Fine. Thanks and we'll begin this morning's program and I understand we'll begin with Dr. Pratt.

DR. PRATT: Good morning and welcome everyone. My name is Douglas Pratt. I'm the Chief of the Clinical Trials branch in the Division of Vaccine and Related Product Applications in the Office of Vaccines. Today, the Committee will see and hear presentations from the Applicant, MedImmune, and from FDA reviewers about the safety and effectiveness of FluMist in a Pediatric Population Less than 59 Months of Age.

In this introduction and background, some of the regulatory history of FluMist will be reviewed beginning with the currently approved indication. Discussions of the VRBPAC meetings of 2001 and 2002 will be summarized. Dr. Robert Daum was chair of these two advisory committees and he's been invited back today and will be available to

share his insights and recollections from those two meetings.

FluMist was licensed in June of 2003 after the second VRBPAC. In January of this year, a liquid formulation of FluMist was approved. This is relevant to today's discussion because the main studies to support the age and indication below five years of age were conducted using the liquid formulation. Relevant post-marketing safety experience from the Vaccine Adverse Event Reporting System will be presented and the Applicant's proposed new indication will be presented. And then to help focus the discussion today, the questions to the Committee will be previewed. Later after the presentations from the Applicant and from FDA reviewers, I will return to say a few words about pharmacovigilance and risk management and then present the questions formally to the Committee for discussion and voting.

The current approved labeling of

FluMist has the following indication: FluMist is indicated for active immunization of healthy children and adolescents five to 17 years of age and healthy adults 18 to 49 years of age against disease caused by influenza types A and B contained in the vaccine.

The current label also contains the following warnings: the safety of FluMist in individuals with asthma or reactive airways disease has not been established; FluMist should not be administered to individuals with a history of asthma or reactive airways disease; the safety of FluMist in individuals with underlying medical conditions that may predispose them to severe disease following wild type influenza infection has not been established.

At the first VRBPAC to discuss licensure of FluMist, Aviron was the applicant. Aviron was seeking licensure

FluMist for the age range one through 64 years. Regarding effectiveness, the Committee voted that efficacy or effectiveness had been demonstrated across the age range. However, the Committee did not agree that the safety of FluMist had been adequately demonstrated. Concerns included imbalances in the number of cases of pneumonia and wheezing in children, lack of information about co-administration of FluMist with other live vaccines administered in the second year of life such as measles, mumps, rubella and varicella and that the large safety study, study 019, was ongoing at the time of the Advisory Committee and that only interim preliminary data were available.

After the first VRBPAC, study AV019 was completed and the final study report submitted to the license application. This study enrolled 9,689 children ages one through 17 years. It was randomized and placebo controlled. The placebo was normal

egg allantoic fluid.

The study was conducted in Northern California Kaiser which made use of their electronic database to query for medically-attended events that included clinic, emergency room visits and hospitalizations. Medically-attended events were collected for a period of 42 days after a vaccine dose. The main finding of that study was an increased risk of asthma and wheezing diagnoses in children less than five years of age.

Although enrollment was not stratified by age in study 019, subgroups analyses were prespecified based on age. In the prespecified age group 18 through 35 months after dose one, there were 10 medically-attended events for asthma or wheezing after FluMist and none in the placebo group. This is in the setting of all clinic visits, emergency rooms and hospitalizations combined. The lower 90

percent bound on the relative risk was 1.95, however, the estimate in the upper bound could not be calculated because of zero cases in the placebo group.

Combining doses one and two, there were 16 asthma events in the FluMist group and two in the placebo group. Again, this is a 2:1 randomization. So the event numbers cannot be compared directly, but the relative risk estimate was 4.06 with a lower 90 percent bound above one. Analysis in this 18 to 35 month age group was prespecified, however, to determine if the risk of asthma extended beyond this age group, a post hoc exploratory analysis was done.

In this analysis of asthma events after dose one, age groups were augmented in six month increments starting from 12 months of age and the relative risks were calculated for the cumulative age groups. Although exploratory, the risk of asthma events appeared to increase up to 59 months of age

at which point the relative risk estimate was 3.53 and the 90 percent lower bound was above one.

With knowledge of these safety data, the Applicant elected to restrict the age indication being sought to individuals five through 64 years of age and acknowledged that additional studies were needed in children under age five to evaluate the safety of asthma and wheezing.

So at the second VRBPAC which was held in December of 2002 to again consider the data provided to support the licensure of FluMist, this time MedImmune was the applicant and the requested indication was now for persons five through 64 years. The completed study of 019 safety data were presented at the meeting. This time the Committee was asked to vote on the adequacy of the safety and effectiveness by age groups and these age groups were age five through 17 years, 18 through 49 years and 50 through 64

years.

At this second VBRPAC, the Committee voted that effectiveness or efficacy was demonstrated for ages five through 49 years, but not for the age group of people 50 years and older. This outcome was not entirely consistent with the vote of the previous VRBPAC. On the question of the safety, the Committee voted that the safety had been adequately demonstrated in the age group five through 64 years.

So FluMist was licensed in June 17, 2003 and at that time, MedImmune agreed to conduct an open label, multi-year clinical safety study on 60,000 FluMist recipients, 20,000 of each of the following age groups: five through eight years, nine through 17 years, 18 through 49 years. Safety outcomes to include asthma, wheezing, all medically-attended adverse events, serious adverse events including deaths and rare adverse events potentially related to wild-type

influenza infection were to be assessed. The final study report for this post marketing study is anticipated in 2011.

As mentioned earlier, the FluMist liquid formulation was approved in January of this year. This formulation can be stored at refrigerator temperatures for up to 18 weeks but not beyond June 30th for a given influenza season. The volume of the dose administered is 0.2 cc as compared to 0.5 cc of the frozen formulation. The change was supported by potency of the product through the dating period and by clinical data in adults and children ages five through 49 demonstrating similar immunogenicity as to the frozen formulation. Again, this is relevant because it's the liquid formulation that was studied in the studies that will be discussed today for children under five years.

Since licensure of FluMist, the post marketing safety reporting has been tracked through the Vaccine Adverse Event

Reporting System known as VAERS. The slides I will present use VAERS data current through February 28, 2007. I would like to thank Drs. Hector Izurieta and Wei Wa for assembling these tables.

The first table shows adverse events reported by age groupings. Of note is that few reports have been received for children under age five years and only a single report received a child under two years.

This is a somewhat busy slide which shows outcomes of interest by age grouping. So I would focus your attention to the first two lines in red which show that of the few reports in children under age five none were due to asthma, pneumonia or other main outcomes of interest. Thus, based on the VAERS reporting, the current age restriction on the label indications appears to have been successful in avoiding respiratory events and other serious adverse

events in young children.

This slide of VAERS data shows reports of asthma in persons with a history of asthma or wheezing. It can be seen that despite the warnings in current labeling about use of persons with a history of asthma, these warnings were not entirely effective in avoiding use of FluMist and reports of asthma in persons with a history of asthma following use of FluMist.

When discussing VAERS data, the limitations of VAERS must be acknowledged and these include that VAERS is a voluntary passive surveillance system there is risk of under-reporting and reporting bias.

At this time, I would like to present the proposed label indication. The proposed indication that the Applicant included in the VLA supplement submission reads as follows: "FluMist is indicated for active immunization of individuals one through 49 years of age against influenza

diseases caused by Influenza Types A and B contained in the vaccine." In subsequent communications between FDA and the Applicant, modifications of the indication have been proposed and also in the slides that Applicant will show today a modification of this indication will be shown. But the final indication and limitations on the indications and warnings will be decided in labeling discussions between the Applicant and FDA taking into consideration comments from the Committee's discussion today.

So today is the third VBRPAC to discuss FluMist. At today's meeting, data from additional clinical studies that have been submitted in the license supplement application and are intended to support use of FluMist in children under age five will be presented and discussed.

The main study of efficacy and safety is study MI-CP111. It's a comparative efficacy and safety study of liquid FluMist

versus TIV in children six to 59 months of age. Just this is a more detailed discussion of the study design. I think I'll leave this for reference. Others will discuss this study in more detail. I'll only point out the study enrolled 8,475 children about half of whom were from the U.S.

At this time, I'll present questions to the Committee as a preview in order to help focus the discussion later today. There are three questions. The first is do the data demonstrate the efficacy of FluMist for prevention of influenza illness in the following: (a) in the Applicant's proposed population, that is children age 12 to 59 months without a history of wheeze; (b) children in the age strata six to 23 months; (c) children in the age strata 24 to 59 months.

The second question, do the safety data demonstrate that the benefits will exceed the risks of FluMist for use in (a)

the applicant's proposed population, that is, children age 12 to 59 months without a history of wheeze; (b) children in the age strata six to 23 months regardless of wheezing history; and (c) children in the age strata of 24 to 59 months regardless of wheezing history.

And the third and last question, if approved for children less than five years of age, what additional post marketing studies or surveillance activities would you recommend? Again, I will come back later in the day and present these questions again for formal voting. Thank you. That concludes the background and introduction.

ACTING CHAIR MODLIN: Thank you, Dr. Pratt. I think we'll proceed on with the company's presentation and who will be leading off? Will it be you, Dr. Connor?

DR. CONNOR: Good morning. I'm Ed Connor. I'm the head of Clinical Development and the Chief Medical Officer at MedImmune

and today I'll be discussing the safety and efficacy data that support our proposed indication for FluMist for children under five years of age. Obviously, while I'll be making the presentation, I speak on behalf of a large group of the MedImmune project team, several of whom are here today including Dr. Bob Walker who is the lead for the FluMist project, Dr. George Kemble who is the head of Research in MedImmune vaccines in California and Iksung Cho and Micki Hultquist who are the statisticians for the project.

In addition today, we have additional outside advisors and investigators. They include Dr. Bob Belshe and Kathy Edwards. Bob was the PI of the original placebo-controlled trial for FluMist in young children and is the PI for the CP111 trial. Kathy Edwards is a professor of pediatrics and one of the steering committee members for the CP111 study. Dr. Dereck Weycker is an outcomes research expert who

works for Policy Analyses who was the agency that we used to do an outside assessment of risk and benefit. Dr. Janet Wittes who is senior statistical consultant and Pamela Zeitlin who is the head of Pediatric Pulmonology at Johns Hopkins.

What I'm going to do this morning is to after some brief introductory comments review with you first the data on efficacy for FluMist in children under five years of age and then followed by a summary of the data on safety of FluMist in children under five years of age, a bit about our post-marketing plans and then some final conclusions.

Why way of introduction, it goes without saying in this audience that influenza is an important respiratory pathogen. Influenza is the leading cause of vaccine-preventable morbidity and mortality in the U.S. Vaccination is the primary method of preventing illness and severe

complications due to flu and despite the best laid plans of predicting a vaccine match, antigenic mismatch between vaccines and circulating strains is common and complicates influenza prevention.

With regard to influenza in children, the rates of influenza infection are actually highest among kids. Hospitalization rates, for example, in young children are similar if not sometimes higher than hospitalization rates in the elderly. In addition, there's a significant burden of morbidity in kids, both in the outpatient setting and the ER as well as in outpatient visits.

Annual vaccination is currently recommended for all children between six and 59 months of age in the United States and trivalent inactivated vaccine is currently the only available licensed product for children under five and there's a single manufacturer for TIV in children under four.

FluMist as has already been characterized is a live, cold-adapted, temperature sensitive attenuated influenza virus vaccine. It is trivalent. It contains as the trivalent inactivated vaccine an H1N1 and an H3N2 and a B strain. Each dose of vaccine contains 10^7 fluorescent focus units of each strain and the current formulation which is the refrigerated formulation of FluMist the dose is 0.2 mLs which is 0.1 mLs per nostril by internasal spray. The current storage conditions are between 2 to 8 degrees Centigrade in the refrigerator and the vaccine contains no preservative, that is no thimerosal.

Dr. Pratt already reviewed the regulatory history. Briefly again, FluMist was approved in the frozen formulation in 2003 in healthy individuals between five to 49 years of age. Between 2003 and 2007, commercial product was available and distributed and safety data were collected

during that time and in January of 2007, the refrigerated formulation was approved for the current indication which is healthy individuals five to 49 years.

With regard to post licensure safety, the VAERS data has already been reviewed for you. Within the five to 49 population, there have been about seven million doses that have been distributed for commercial use between 2003 and 2007 and no new safety signals have been identified since licensure by reviewing both the VAERS data for the first two seasons and the ongoing post-marketing safety data that we've been collecting currently in 45,000 of the 60,000 planned enrollment into that study.

Now again, MedImmune originally with the first indication, the first application, for FluMist did not seek licensure for children under five. The reason was what Dr. Pratt has already reviewed which is that in the original

placebo-controlled safety study that was done in Kaiser there was a safety signal that was identified for wheezing in young children and then ultimately post hoc analyses were done up through 59 months and what we observed was an increased relative risk for wheezing or asthma and wheezing in that population. The limitations of that study were that the ascertainment of the outcome was from database coded terms. So it was a little bit more difficult to distinguish exactly what those outcomes were and the study wasn't specifically designed to look at rates of asthma and wheezing in a prospective way. So we believed at that point that further data were needed to understand the safety signal. There weren't other trials that addressed this issue specifically at that time.

Since that time, there has been some additional background data that's both been published and then collected by various parties. There have been two published

studies that have suggested better efficacy of FluMist compared to TIV that have been published. These are studies that were conducted by Wyeth outside the U.S., not under the U.S. IND and included a study in six to 71 month old children with recurrent respiratory tract infections and a study in six to 17 year old asthmatics. Both of those studies were about 2,000 patients in size and what we saw in those trials were a 53 percent and a 35 percent rate of fewer cases of influenza in the FluMist group compared to the TIV group at a time where predominantly matched B strains were circulating. We did not see safety signals in those trials and as I mentioned, these were open label studies not done under the IND, conducted outside the U.S., but were useful background information and planning for what to do going forward in children under five.

There were a number of IND studies of safety and efficacy that were conducted in

children under 59 months of age or younger and those included the original study AV006 which was conducted under a CRADA with the NIH with Aviron. A placebo controlled trial P501 which was conducted by Wyeth under the U.S. IND and then ultimately the study CP111 which we're primarily here to talk about today.

Based on the data from those studies and I'll review all of this data with you, we believe that we've been able to demonstrate high levels of efficacy of FluMist against influenza, significantly higher efficacy compared to TIV in CP111. We've seen cross protection against mismatched H3N2s and in 111, better cross protection compared to TIV. And then on the safety side, our assessment is that further evaluation is still needed in the six to 11 month old population and in children 12 to 59 months with a history of wheezing and we'll get into that in some detail as I go forward.

For children without a history of asthma or wheezing, we believe we've established safety for children 24 to 59 months and that the risk/benefit analysis in children 12 to 59 months warrants availability of the vaccine in that population.

We've fundamentally come to this point requesting that the available population for vaccination with FluMist be expanded to include children 12 to 59 months of age without a prior history of asthma and wheezing.

What I'm now going to do is turn to a review in the next few minutes of the efficacy data of FluMist in children under five years of age to support the conclusions that I've just talked to you about.

There were two placebo controlled trials that were conducted that assessed efficacy against all three strains of influenza including a mismatched H3N2. Those two studies were AV006 and P501.

AV006 was a 1600 patient trial. It was conducted between 1996 and 1998 in the U.S. It was a randomized, double-blind, placebo-controlled study in children 15 months to 71 months of age. Each of these trials were conducted over two consecutive influenza seasons and for AV006 in the first season, matched A/H3N2 and Bs were circulating and in the second year, almost predominantly a mismatched A/H3N2 A/Sydney was circulating.

Study P501 was a trial conducted in 3,174 children. It was done during the 2000 to 2002 influenza season in eight countries in Asia. It, too, was a randomized, double-blind, placebo-controlled trial in children 12 months to 35 months of age. In the first year of that trial, matched H1s, H3s and Bs were circulating and in the second year of that trial, a matched H3 was circulating.

This slide shows the efficacy data

from the first year of that trial for the primary endpoint. So the primary endpoint in the study were matched strains and here in AV006, you see the efficacy against any strain over 90 percent for the matched H3s which was 96 percent and for B approximately 91 percent. For Study P501, you see the overall efficacy at 73 percent, 80 for H1s, 90 for H3s and 44 for B.

These data, this slide shows the efficacy in the second year of both of these trials. Here for the AV006 study as I've mentioned, predominantly what was circulating was mismatched virus. Efficacy against the mismatched A/H3 was 87 percent and in the P501 trial, a matched H3N2 was circulating and efficacy was approximately 85 percent. So based on these placebo control trials, we believe that we've demonstrated high levels of efficacy of FluMist against influenza and these trials were conducted in geographically devise areas over different times and they

were also obviously in somewhat different populations of children.

Now based on the observations from the placebo-controlled trials, based on the published data regarding the potential advantage of CAIV-T or FluMist over TIV and the original safety observation from AV019, we then designed and conducted a pivotal comparative trial that head-to-head compared FluMist and TIV. The goal of the study was to evaluate the safety and efficacy of FluMist compared to TIV and allow assessment of the risks and the benefits of both vaccines in children between the age of six to 59 months.

MICP111 was a randomized, double-blind, TIV-controlled trial. It was a trial done in a double-dummy design. So everyone got an injection and everyone got a nasal spray, either placebo or active and it was a multi-national trial that was done in the U.S., in 12 countries in the Europe and the

Middle East and in three countries in Asia. Children that were enrolled in the trial were between six and 59 months of age. The total enrollment was 8,475 and essentially all children were included. The excluded children were if you recently wheezed, so if you had wheezing within the previous six weeks, if you had a history of severe asthma as benchmarked against the NHLBI criteria and if the investigator judged that you were immunocompromised.

The stratification factors for the trial included age, country, previous influenza vaccination history and history of three or more wheezing episodes. The population of interests were children between six and 23 months and 24 months and above because at that time when the trial was first conducted, the recommended population for influenza vaccination was six to 23 months.

The group between 24 and 35 months were included as a stratification variable to

balance those children receiving different dose formulations of TIV. TIV in children less than three is 0.25 mL dose. The prespecified analyses for children was six to 23 months and 24 to 59 months and again because originally the recommendations were for six to 23 month of age children, the enrollment in that population was increased to allow a robust assessment of that younger age group.

The primary efficacy endpoint was culture-confirmed, modified CDC-ILI that was caused by matched strains. The definition of CDC-ILI was modified slightly. The definition is listed here. It is increased temperature. It's basically a febrile illness with cough and sore throat. What was added to that definition was runny nose or nasal congestion in light of the fact that obviously sore throat is difficult to ascertain from this age group child and these findings had to be on the same or consecutive

days.

In order to be able to meet the definition, symptoms must be within plus or minus seven days of a positive culture and what I will show you are analyses that are done according to protocol population as well as the intent to treat population which are effectively all randomized kids.

First of all, there were 4,232 children randomized to the TIV group and 4,243 to the FluMist group. The baseline characteristics between these groups were balanced at entry. The average age of patients was about 26 months. There were just over 50 percent of the population that were male. Most were white, non Hispanic. About 22 or 23 percent of children had received a previous vaccine. And by the stratification variable a prior wheeze that was three or more, there were about six percent in each group and about 21 percent of the population who had any prior history of

wheezing.

In addition to the baseline characteristics, the follow-up of patients was balanced between the two treatment groups. The median duration of follow-up was 219 days in each group. The numbers of patients in the two dose group who received two doses was 94 percent and 93 percent. There were over 20,000 swabs collected during the course of the trial, about 10,000 in each of the groups and the average number of swabs per a patient for 2.4. Of the cultures that were taken, the proportion that were taken within 24 hours of symptoms were about 87 and 85 percent of the population.

This slide illustrates the circulating strains during the 2004-2005 influenza season. That was the time during which this trial was conducted. First of all for H1s, there was an A/New Caledonia that was circulating that was in the minority in the U.S., about 19 percent in Europe. For

A/H3s, there was a Wyoming circulating that was actually in the minority, but a mismatched A/California that was circulating in both Europe and the U.S. had a reasonably high frequency. For Bs, B/Yamagata both matched and mismatched were circulating and a smaller fraction just under 10 percent of a lineage difference that is B/Victoria lineage was circulating at about just under 10 percent.

This slide shows the time course of the conduct of the trial. Children were randomized and received their first vaccination and all their immunizations were completed by the end of October in 2004.

And then over the course of the season, this slide illustrates the number of culture confirmed, modified CDC-ILI caused by any wild-type strain and over the course of the trial, there were 153 cases in the FluMist group and 338 cases in the TIV group.

These next series of slides

illustrate the primary efficacy outcomes from CP111. They are all basically set up in the same way in which the attack rate is on the Y-axis. Below on the X-axis are the strains that we're analyzing. The number of cases in each of the groups are listed at the bottom and the total number of children that are in each of the randomized groups are at the far bottom.

This is the analysis of the primary endpoint which is the ATP analysis for matched strains in which we saw a 2.4 percent attack rate in the TIV group and a 1.4 percent attack rate in the FluMist group, a 45 percent reduction that was statistically significant. Next to that is one of the secondary endpoints which was the mismatched, modified CDC-ILI and there you see a 6.2 percent rate in the TIV group and 2.6 percent in the FluMist, a 58 percent reduction which was also highly statistically significant.

On the second part of this slide,

you see the same analyses as here except done with the ITT population. The ATP population was about 93 percent of the ITT population and the primary reason for any differences in the numbers was children who did not get a second vaccine and those were balanced between the two treatment groups. So fundamentally, you see that the analyses, the results, the differences are fundamentally the same between ITT analyses and ATP analysis.

This slide now shows the all-strains analysis. So as I told you, a predominant part of the circulating virus at that time was mismatched A/H3 and what you see an 8.6 percent attack rate for all influenza strains in the TIV group and a 3.9 percent rate in the FluMist group. This is constructed so that the hatched line are the mismatched outcomes and the solid bars are the matched outcomes.

If you then look at that efficacy

by strain, you see that for H1N1s there were smaller numbers. These were all matched viruses and there was an 89 percent reduction which was statistically significant. For the H3s, 4.5 to 0.9, 79 percent reduction which was statistically significant and for the Bs, a 16 percent difference which was not statistically significant.

This next slide shows you the analyses of efficacy for the primary endpoint by the two main subsets of patients. That is children between six to 23 months and 24 to 59 months. And here you can see that for the primary endpoint in the younger age group, there was a 30 percent reduction which was not significant. There was a 53 percent reduction in the older age groups with a highly statistically significant P value. These are just for matched strains.

When you look at the all-strains analyses for above and below two years of age, you see effectively the same reduction

in the six to 23 month category as you do for the 24 to 59 month old children. So these are all strains 7.2 to 3.2 and 9.8 to 4.5 in the two subsetted age populations.

This last efficacy slide shows the other illnesses that were associated with influenza culture that we saw reductions in. So here you see again the slides are set up the same way with matched and mismatched stacked. These are all strains against symptomatic influenza. Symptomatic influenza refers to any symptoms even if it did not meet a CDC-ILI definition and there was a 50 percent reduction there. For LRI associated with influenza, there was a 45-46 percent reduction and in AOM a 50 percent reduction and each of these were also statistically significant. These are outcomes that are associated with influenza positive cultures.

Now I'm going to switch gears. First of all, from an efficacy conclusion perspective, we believe that from these

trials we've been able to demonstrate high levels of efficacy against influenza. We've been able to show in CP111 that there is significantly higher efficacy in the CAIV-T group or FluMist group compared to the TIV group and that we've seen cross protection against mismatched A/H3N2s in the placebo-controlled trial AV006 and better cross protection against A/H3s in CP111.

Now I'm going to change gears and leave the efficacy evaluation and move to a summary of the safety data in children under five. What I'm going to review are the following. I'll show you data on reactogenicity and adverse events. We'll talk about mortality, serious adverse events, the wheezing outcomes that were one of the primary outcome of interest in the trial and a risk/benefit assessment.

First of all, reactogenicity. Basically, in CP111, we saw for both vaccines the reactogenicity profile that one would

expect. We saw a slightly higher rate of injection site reactions, a significantly different rate in the TIV group and remember, all kids got an injection. One was placebo and one was active drug. We saw a higher rate of runny nose and nasal congestion and a higher rate of low grade fever in the FluMist group compared to TIV and I've shown you here the higher rates of fever for comparison. There were no differences in those groups, so fundamentally, a higher rate of site of injection reaction in TIV, a higher rate of nasal congestion and runny nose and low grade fever in CAIV-T or FluMist which was typical of what we'd expect with the vaccines.

This slide shows you the collection of adverse event data. So these are any changes from baseline for children that are -- for the population but through 28 days which is when the adverse event collection time frame was managed. What we saw were approximately 30 percent of children

in both groups had at least one adverse event. Adverse events with a difference of greater of one percent which are a typical labeling threshold had sneezing a little higher in the FluMist group and diarrhea, otitis media and rash a little higher in the TIV group, but none of these differences were any greater than 1.5 percent differences. So in effect, they were, if there are any differences at all, they were small.

For severe adverse events and related adverse events, those were balanced between the two treatment groups. There were a small number of children in each group that did not receive a second vaccination because of an adverse event or a reactogenicity event. That was 0.8 percent in the TIV and 1.1 percent in the FluMist group.

For mortality, mortality was, from as you would expect in the population that was enrolled in the study, mortality was low. There were two deaths that occurred on

study. Both were unrelated to study drug. One of them in the FluMist group was a one year old who died of a foreign body aspiration which was a toy and in the TIV group, there was one death which was a two year old who died in a house fire.

Now the next series of slides, we'll review for you a description of the safety analyses for looking now at SAEs and hospitalizations and the time period of reference is through 180 days after the last dose. This is the time period during which serious adverse events were collected. What we saw was overall SAEs were similar between the two treatment groups. That is 3.1 percent in TIV and 3.3 percent in FluMist. As is typically the case, hospitalizations represent the biggest thing that meets the definition of an SAE. Ninety-four percent of all of the SAEs were hospitalizations.

What we found when we analyzed these hospitalizations in an exploratory way

looking at all sorts of various parameters was increased hospitalization rates in the FluMist group between six to 11 months of age. So when I look at it in this graph children six to 11 months and then by year interval thereafter and I look at overall hospitalization rates by age and these are hospitalizations that go throughout the 180 day period, what I see is a statistically significant difference in six to 11 month of age kids and specifically no difference in the two groups as you get from 12 months and above.

If I look at this group to try to analyze whether or not this 11 month threshold is the correct threshold or not, on the next slide what I show are by age, month, from six months to 24 months, the frequency or the percentage of subjects with a hospitalization and what you can see is up to about 10 months of age there's a higher rate in the FluMist group compared to the TIV

group. Beyond approximately 10 months of age, there are scatter above that age. So there really are not any differences as I showed you in the previous slide. So from our perspective, there is an observed increase in hospitalizations between six and 11 months of age. That is limited to the six to 11 month of age kids and not seen above that age group.

This slide shows you the hospitalizations in the six to 11 months of age children where we saw the increase by the type of hospitalization and what you see here are hospitalization diagnoses for lower respiratory tracts. Primarily, these were coded terms as either pneumonia or bronchiolitis. The principal coded term was pneumonia for lower respiratory tract illnesses, GI, other infections and then all the other causes. And when you look here, what you see is an increase in the FluMist group. I've already told you that there's an

increase in six to 11 months overall in that population, but you also see that the increase is scattered across all of the diagnoses. So the diagnoses that landed the child in the hospital were typical childhood diagnoses of respiratory and GI disease. That's what normally puts that age kids in the hospital and that while there was a higher rate in the FluMist group, the distribution of those were across all of the major diagnoses.

The other thing that we looked at was the temporal distribution of hospitalizations and this slide just illustrates the TIV group and the FluMist group from the time of randomization through 180 days after the last dose and what you see here is a nontemporal distribution, that is, no temporal distribution of the hospitalizations among the TIV or the FluMist group following vaccination.

I didn't include the slides that

break down each of these categories by that same type of event, but in fact, we have those and there really are no temporal distributions that we can observe for each of those other categories whether you look at respiratory, GI or other categories. So it is based on the observation of the increased hospitalizations that were observed in this trial between six and 11 months that led us to not seek an indication in the six to 11 month old patients until we did further evaluation of that group.

Now in addition to looking at age, which we explored as part of the hospitalization outcomes, we obviously in exploratory analyses looked at multiple other variables and factors that could be associated with safety outcomes and one of the things that we were interested in because of the issue of asthma and wheezing was whether or not a prior history of wheezing or asthma influenced the safety outcomes in any

way and we actually had collected this prior history of asthma and wheezing prospectively as part of the case report form at the time the children were entered into the study. That was collected both from the parent and from the investigator and we identified that about 21 percent of children using these relatively simple questions of whether or not either asthma or prior wheezing had been identified were identified as having yes to that answer.

When we looked at the sources of that information, all of this was collected as part of the case report form definition, about 85 percent of the time this factor was identified by the parent. Obviously, many times when the parent identified it, the physician also identified it and in 15 percent of the cases, it was identified by the health care provider but had not been identified by the parent.

When we looked at the answer to

whether or not the parent or health care provider had identified a prior history of asthma or wheezing and applied that to the hospitalization data, what we found was that a prior history of asthma or wheezing appeared to be associated with a higher hospitalization rate.

This slide shows you the hospitalizations by age for children with a history of asthma and wheezing through 180 days after their last dose and what you see here on the left is children without a prior history and on the right, children with a history. This is representing about 80 percent of the total population. About 20 percent of the total population as I mentioned earlier had a prior history of wheezing. You see in both of these categories children six to 11 months the prior observation which was that there was a higher rate of hospitalization six to 11 month old children and what you see in the

children who did not have a prior history of wheezing was no increase in that population. In fact, the FluMist group are actually lowered than the TIV group and in children with a history of wheezing, you see this persistent increase or observed increase in children between 12 and 47 months of age.

Now we interpret these analyses with significant caution because these are post hoc, multiple exploratory analyses. But it was based on this observation and the fact that children with asthma are already excluded from the label above five years of age that we chose not to include this population in the proposed indication and this population, the majority of kids between 12 and 59 months is the population that we are asking for an indication for.

From an SAE and hospitalization perspective, we believe that further evaluation is needed in six to 11 months of age. We intend to continue to study those

children principally with lower doses of vaccine. We also believe that for children 12 to 59 months of age while the distinction between those children with and without a history of wheezing is not proven but simply the observation that I showed you we believe also that in this category as well as other children who have a known history of asthma or other underlying lung disease that we need to continue to evaluate those children in a risk/benefit way. But we did not see any SAE or hospitalization increase in children 12 to 59 months of age who did not have a prior history and, in fact, in this population, the risk of hospitalization was higher in the TIV group compared to the FluMist group.

Now I'm going to change from the SAE analyses to the wheezing outcomes analysis. So wheezing as an outcome was obviously of significant interest as part of the followup evaluation from the AV019 trial and so in CP111, we defined a case definition

for wheezing so that the two groups could be compared using that case definition. The case definition we called protocol defined, medically-significant wheezing or MSW and the definition that was used to track patients for this case definition was wheezing on physical examination plus at least one of the following. They either needed to have a new daily bronchodilator use or observation of respiratory distress or hypoxemia.

The way that this was ascertained was that parents were instructed to have the child seen by a health care provider for any respiratory illness including wheezing. That's part of the evaluation for efficacy as well as the evaluation for safety. And although parents were instructed to bring the child to the health care provider, the diagnosis of hearing wheezing was left to the health care provider obviously and treatment was at the discretion of the physician, not prescribed by the protocol.

In addition to this case definition which was prospectively defined, we also collected any reports of wheezing and any reports of wheezing included anything that was reported by either the parent or the investigator whether it was confirmed or not. It also was not a prespecified case definition. It was an adverse event data collection tool primarily. It included medically significant wheezing as well as all other events. The prespecified interval for the analysis of wheezing outcomes was from randomization through 42 days after the last dose.

This is what we found with regard to wheezing outcomes in the whole population. What we observed was that there was an increase of signal for wheezing in children six to 23 months of age and there was no increase in children 24 to 59 months of age. So here you see the graph for protocol-defined wheezing and for any wheezing for

children six to 23 months and on the right-hand side, 24 to 59 months. You can see that there were statistically significant differences in protocol-defined wheezing and in any wheezing in the younger population, but we saw no differences in children 24 months of age and older.

Just like with the other question, the question is is 24 months of age the right threshold. It was certainly the prespecified analysis for each of the treatment groups. But we looked here, it's hard to see the numbers at the bottom obviously, but these are from six months to 59 months of age the monthly differences between the two groups or percentage of children with, in this case, MSW and what you can see is that in children under two years of age, first of all, there are higher rates of wheezing, that's a pretty well-known fact, compared to older children and then secondly, they increase in the FluMist group as seen really isolated to the

under 23 month of age kids. We don't see that spilling over to the other age groups. So the observation of seeing medically-significant wheezing increases in the children that were under 24 months of age is truly in this population of six to 23 months.

Now another question that arises is assuming that we've demonstrated that there are in children under 24 months of age a higher rate of wheezing in FluMist recipients compared to TIV, the question is raised about so what are those episodes, what are the characteristics of those episodes and how severe were they. And these episodes were tracked through the trial in a prospective way and I'll go through that for you here for medically-significant wheezing for the whole population of children under 24 months of age.

In this population, what we saw was a total of 192 children who had an episode of MSW. There were 75 in the TIV

group and 117 in the FluMist group. There were 14 children that were hospitalized associated with MSW, four of 75 in the TIV group and 10 of 117 in the FluMist group, so a little numerically higher rate in the FluMist group and this is about five percent versus eight percent. But this analysis is also complicated by the fact that there were some of these cases that had alternative diagnoses. The alternative diagnoses were not captured in every case that was hospitalized, but here we know that at least three of these kids and three kids in actually each of the groups had an alternative pathogen identified and it was predominantly RSV during the time of follow-up.

Of these children, there were no ICU admissions and no mechanical ventilation associated with MSW and if you look at a different level, that is, how many children met the definition of MSW, purely by having a

new bronchodilator, that is, that they did not have respiratory distress or hypoxemia, that was 69 percent of the cases in TIV and 75 percent of the cases in FluMist.

The other question related to this group is if a case of MSW was identified is there evidence that there's recurrent episodes beyond that and we looked at recurrent wheezing through 180 days after the last dose for the children who had MSW and we saw a 28 percent rate in the TIV group when we counted one additional episode compared to 32 in the FluMist group and when you look at two additional episodes, five percent in TIV and four percent in FluMist. So overall, we saw a numerically higher rate of hospitalization, but did not see, but those hospitalization analyses are a little complicated, overall major differences in the two groups with regard to severity.

Now the group under 24 months represents the prespecified analysis group in

the trial, but the group that is included under 24 months in the indication that we're seeking are children 12 to 23 months because of the observation that eliminated the six to 11 month old kids. So I'll just briefly go through with you in the remaining 12 to 23 months without a history of asthma or wheezing the kids that are under 24 months of age and in our proposal. There were in that group 58 children, 23 in the TIV group and 35 in the FluMist group. There were only three children that were hospitalized, one in TIV and two in FluMist and one in each group had an alternative etiology identified.

When you look at how they met the definition, there were 74 percent of cases in TIV and 86 percent of cases in FluMist that met the definition simply by a bronchodilator and not respiratory distress or hypoxemia. And when you look at recurrent wheezing through 180 days the rates were lower in FluMist compared to TIV regardless of which

of these definitions you used. So in the population of children who we actively followed through the 180 days who had medically-significant wheezing below 24 months and were in the population that we're proposing, we didn't see any evidence of severity increase in that population. The episodes were primarily an episode of wheezing associated with bronchodilator use.

Our conclusions regarding wheezing are that wheezing is not increased in 24 months of age or higher, that there appears to be an increase in wheezing in children 12 to 23 months of age without a prior history of wheezing and it's this residual wheezing in the 12 to 23 month age category that is under consideration here this morning.

Now I'm going to end the efficacy/safety discussion by reviewing with you a view of the risk/benefit analysis of FluMist relative to TIV and for this, we sort of have to change the perspective that we're

looking at from what I've shown you before to a data display which includes the following. So this is designed to assess the overall risks and benefits of FluMist and TIV using the data from CP111. The data that I'm going to show you are the rate differences, that is, FluMist minus TIV per thousand children in order to be able to normalize the denominator for the risk and the benefit.

The safety endpoints that we assessed were the safety endpoints of interest that I just spoke about and we look at those safety endpoints from the time of randomization through 42 days which are approximate to the vaccination and through 180 days because 180 days is the time frame of the efficacy analysis and in order to be able to look at apples-to-apples time frames 180 days was chosen.

The analysis that we have done is culture confirmed, modified CDC-ILI from randomization through 180 days based on all

the cases because both matched and mismatched strains were the strains that were circulating and that was the benefit that we observed in the trial and the summaries that I'll show you are for 12 to 23 months and for 24 to 59 months without a history of wheezing because that's the population that we're interested in.

Okay. So this slide is fairly complicated. I'll spend a minute just going through and getting you oriented to what we're showing. Again, these are CP111 results. There are event rate differences, FluMist minus TIV per 1,000 children, with their 95 percent confidence intervals. They are for children without a history of wheezing and asthma; that is, this is the population that we are proposing to include in the label and there are two graphs, one of them for 24 to 59 months and another for 12 to 23 months.

What you see in both of the graphs

is a zero line which is no rate difference and then a reduction of cases above the line which is benefit and an increase in cases which is below the line which is risk. And what we see in each of these categories are analyses through 42 days and through 180 days after the last dose.

The way the slides are set up is that the rate difference is the dot, the 95 percent confidence intervals are shown and we look at outcomes through 42 days for any wheezing, for medically-significant wheezing and for all-cause hospitalization and then for 180 days for the same outcomes and then on the far end of each slide is the benefit which is modified CDC-ILI for all cases. So in this analysis, one would see that there are about 49 cases, these are 24 to 59 month kids, of benefit that is prevention of modified CDC-ILI in children 12 to 59 months without a history of wheezing and that in the same time frame of 180 days, you see

basically a reduction of hospitalization of eight per thousand, of medically-significant wheezing of six and of any wheezing of eight with confidence intervals.

If you look not at 180 days compared to 180 days, but you look at 42 days proximate to the vaccination compared to the 180 day outcomes, you see that those rates are about six benefit for hospitalizations and then you can see one and minus three for wheezing. So in children 24 to 59 months of age without a history of wheezing, we really don't see any -- We see benefit and we see no signal of additional risk.

The difference between this and children with a history of wheezing, I'm not showing you in this primary presentation but I can show you if you're interested, the distinction in these populations are smaller. But when you get to 12 to 23 months for children without a history of wheezing, what you see in light of this is that you see 35

cases of benefit in the 180 day analyses, you see eight savings of hospitalizations for excess cases of medically-significant wheezing, seven for any wheeze through 180 days. If you look at 42 days, you see the numbers shift a bit, three for hospitalization, 12 and 18, respectively, for MSW and for any wheeze.

While this analysis is only one analysis of many that you can do of this kind of type and various folks have looked at it in various different ways, our assessment is that among this population of 24 to 59 months children we don't see any significant safety risk and we see benefit. In the 12 to 23 month category, we see benefit. We see some hospitalization reduction, but there is some residual medical wheezing cases and those cases are defined in terms of severity as episodes that are associated with bronchodilator therapy and that's the characterization of that illness.

From a safety summary perspective, we believe that the reactogenicity of FluMist is as expected, that we need to continue to evaluate children six to 11 months perhaps with a lower dose of vaccination, 12 to 59 months without a history of wheezing because of the analysis that we've done but also because effectively children with wheezing and asthma are already excluded from the above five population and so consistency also reigns with not vaccinating those kids who might have a history until we do further study there based on the risk/benefit profile. For the 77 percent of the children that were in CP111 who were 12 to 59 months without a history of asthma and wheezing, we believe that for children 24 to 59 months there was significant benefit and no increase in wheezing or hospitalization. For children 12 to 23 months, significant benefit. There appears to be some residual wheezing within 42 days post vaccination in that population.

Now I'll just briefly talk about post-marketing plans currently. As we briefly mentioned before, we currently have an ongoing 60,000 patient trial that's being done in five to 49 ages in the Kaiser system. Those are 20,000 patients in each of three age designations. We would plan and have proposed an observational study similar to that trial in children that are in this younger age group and we would plan enrollment of at least 20,000 children who are FluMist recipients including assessments of hospitalizations and wheezing particularly in the younger kids. In addition to passive surveillance, education and outreach obviously would be also done and that would include the risks included the package insert, FluMist statements in the vaccine information sheet and targeted outreach to health care providers and parents to understand both the risks and benefits associated with vaccination.

So in overall conclusion, clearly influenza causes significant morbidity in children on an annual basis, that influenza vaccine options for children under five years of age are limited, that FluMist represents a highly efficacious vaccine for children under five years of age, 73 to 93 percent efficacy in placebo control trials and 55 percent fewer cases of influenza illness compared to TIV in CP111. We've shown significant cross protection against mismatched A/H3N2 including better protection against mismatched A/H3N2 in CP111.

The safety of FluMist, we believe, has been established in children 24 to 59 months of age without a history of wheezing and FluMist risk/benefit profile in children 12 to 23 months without a prior history of wheezing also warrants licensing of vaccine in that population. Thank you.

ACTING CHAIR MODLIN: Thanks, Dr. Connor. At this time, I'd like to ask if

there are questions regarding Dr. Connor's presentation and I would suggest that we will have plenty of time for Committee discussion later this morning so that we have a relatively short period of time now. We might limit them to questions regarding clarifications and also perhaps any information data that Dr. Connor may have that he didn't present. Dr. LaRussa and then we'll go around. I beg your pardon.

DR. LaRUSSA: Two questions on Slide 15 I think it was, you presented efficacy in a previous study and could you just say something about low efficacy against matched B strains. I think it was 44 percent and then the second question is in Slide 20 you said about 20 percent of individuals had been previously vaccinated, yet I don't think you presented any efficacy data based on previous vaccination history to clarify that.

DR. CONNOR: Let me -- In this slide as you can see as I mentioned there

were two efficacy estimates for Bs, one of them in AV006 which was 90 percent and one of them in Asia that was 44 percent. The epidemiology of B in Asia during that year was a little complicated.

We also have in addition to these B estimates of efficacy other estimates of B efficacy that come from both published trials as well as other trials and I don't know actually if you can put that up, Chris. Right. So here these are efficacy and placebo controlled trials against B. In AV006, I've already shown you those results. This is the P501 result and these are the estimates of efficacy against B in other trials that were conducted that were actually not part of the actual physical submission but have been published or analyzed otherwise. Then there have been several trials including the two published ones that I talked about in which there was a comparison between TIV and CAIV-T in matched

B years and there was that 35 and 53 percent benefit in those populations.

Your second question was?

DR. LaRUSSA: The second question was in CP111 I think --

DR. CONNOR: Previous vaccination.

DR. LaRUSSA: -- I think you said there was previous vaccination history and what was the efficacy stratified by previous vaccination history.

DR. CONNOR: Yes, we've used -- The jargon in the trials were "previously vaccinated" and "not previously vaccinated" which kind of defined whether you were in a one-dose group or a two-dose group. So the analyses have been done by all those various factors and there really weren't any differences depending on what you looked at. I think if you put up this slide you can see this is across each of the age groups. These are efficacy rates in previously vaccinated children. So these are the relative efficacy

for CP111. So the relative efficacy was in this range.

Most of the analyses that we did actually that used either previous vaccination status or other characteristics were very similar between all of the strata and obviously there is a relatively small number of children who were in the previously vaccinated group.

ACTING CHAIR MODLIN: Dr. Farley.

DR. FARLEY: I have a question about Slide 48 where you were showing us sort of the risk/benefit analysis and I'm wondering whether you looked at it in the predefined stratification group of the six to 23 rather than breaking out this 12 to 23 subgroup.

DR. CONNOR: Yes. I'm not sure that we actually have -- I don't have a slide that looks at that distinction because from our perspective once we saw the hospitalization increase we basically did not

pursue the six to 11 population. So the formal risk/benefit analysis hasn't been done with exactly those cuts.

ACTING CHAIR MODLIN: Dr. Daum.

DR. DAUM: Hi. My question goes a little bit to information gathering and I'd like to know a little more about how you obtained information about whether a child was a previous wheezer or not and someone remarked earlier, I think it was Dr. Pratt, that I was invited for institutional memory. I'm a lot older now than I was then which is kind of a weird thing because my memory has actually deteriorated, but I do remember from the Kaiser Permanente data that they excluded kids that were presented way back when that excluded kids because they had a history of wheezing and then went on to wheeze anyway, that they went back to their records and those kids who went on to wheeze anyway and found that in fact a lot of them had been treated for wheezing in a medical encounter

and so I came away from that with the idea that just asking is not terribly reliable. So I'm wondering what you did here and particularly, I'd like to know about U.S. methods of ascertainment and you mentioned that this was a multinational study and I'd like to know about outside the U.S. and whether there were any differences in ascertainment between those groups.

DR. CONNOR: Yes. Obviously, all of us recognized that ascertainment of, first of all, asthma diagnoses in children under three, particularly children under five is complicated and ascertainment of wheezing may or may not distinguish kids who are going to then go on and wheeze.

I think your memory about the Kaiser study is correct. We did a lot of analyses of various pieces of the Kaiser study. But in each time when we did the Kaiser study, the problem was that it was a database driven analysis. Here what we did,

actually if you put up this slide, Chris, was we took questions that we asked at the time of the enrollment of children and the questions were fundamentally does the child have a past history of wheezing and has a diagnosis of asthma ever been made and that question also recorded who said yes or no to the question and what happened was that as you look at that question about 85 percent of the time it was the parent who said yes and 15 percent of the time as I said only the chart said yes. If you simply used that answer, not the answer about whether you could ever prove whether somebody truly had asthma or wheezing in the past, but if you just used the answer to the question did the parent recall that there was wheezing or did the doctor say that there was wheezing, it's that answer to that question that we used to sort the risks and benefits in the two populations.

So from a going-forward

perspective, we would anticipate that those questions and the answers to those questions in obviously not a precise way compared to the trial, but in a similar way to the trial would distinguish the kinds of risks and benefits that we saw here. We did not go back -- We went back and reviewed records as far as monitoring, but it was mostly to confirm the doctor's answer or the parent's answer.

DR. DAUM: I guess the follow-up is in that last statement you made. So among the kids that actually did go on to wheeze after your vaccine, did you go back and see if the parent's information was correct in terms of their recall or did you do any subanalysis in terms of whether the parent's information was correct?

DR. CONNOR: Yes, well, the parent's information being correct was matched against the doctor's answer to that same question and the doctor used the records

or whatever else was available for the outcome. So if you look at the parent saying yes and the doctor saying yes, about 70 percent of the time the doctor and the parent agreed and sometimes there was overlap and sometimes there wasn't.

So when you go back, sometimes the parent said yes and the doctor said no. Sometimes the doctor said yes and the parent didn't remember. But most of the time we did a lot of analyses of these and we also did analyses of what would happen if you just used the past 12 months because remembering in the past 12 months for a two year old is different than remembering in the past 12 months for a five year old. And, in fact, what they're basically remembering is the last 12 months and the last 12 months have been accurate most of the time. So we actually are pretty confident after having gone through all of this that the distinction that we're trying to make is the distinction

that was made in the trial and reproducing the distinction that was made in the trial albeit not necessarily perfect with regard to the truth about whether there ever was a history of wheezing or not is pretty reproducible going forward.

ACTING CHAIR MODLIN: Dr. Jackson.

DR. JACKSON: Just a minor question. Could you clarify what the differences were in the methods of ascertainment of medically-significant wheeze in the one to 42 versus 43 to 180 day periods?

DR. CONNOR: They were the same.

DR. JACKSON: So one to 42 you had a more intensive method or no?

DR. CONNOR: No.

DR. JACKSON: You had diary accords recorded through the whole period?

DR. CONNOR: Yes. We collected the information through the whole period. Before we went into the trial, we specified

zero to 42 as the outcome time, but we continued to collect medically-significant wheezing as a case definition through the 180 days after follow-up. So the ascertainment was the same. It was just whether it was a prespecified time period or not.

DR. JACKSON: Okay.

ACTING CHAIR MODLIN: Dr. Self.

DR. SELF: Yes, my question is on Slide 48 as well, rate differences, risk/benefit. So the rate differences for the safety outcomes expressed as per thousand vaccinees, those seem fairly solid. But for the efficacy outcomes, it seems that that would vary by year depending on the nature of the epidemic, the match/mismatch. So I'm trying to calibrate that those 35 ILI cases relative to the safety outcomes in terms of the annual variation in flu epidemic, does that represent a whopping epidemic year or a very modest epidemic year?

ACTING CHAIR MODLIN: I was going

to ask the same question and like Bob Daum, our memories of severity of influenza seems to be waning pretty rapidly. Maybe Bob Belshe or someone will remember at least halfway the 2004-2005 season was more than one would expect more than unusual season.

DR. BELSHE: 2004-2005 which is the year of CP111 was conducted and was an average to slightly lower than average flu season. AV006 which was the earlier study in placebo control I think was perhaps a little bit more robust. That 35 cases, remember, is relative to TIV. Relative to a placebo, we don't have it in this year but in AV006 we do have two years of data there and that number would be on the order of 70 to 100 relative to placebo.

DR. SELF: And from those studies relative to placebo the comparable safety rates or the safety events?

DR. BELSHE: We don't have the precision in AV006 to examine that. We

looked at safety events for ten days. That was a decade ago.

MS. WALSH: Excuse me. Could you just identify yourself for the record please? Thank you.

DR. BELSHE: I'm sorry. This is Robert Belshe. Thank you.

ACTING CHAIR MODLIN: But, Bob, the presumption would be that the safety events would be no different depending from season to season. Correct?

DR. BELSHE: Yes, I would agree with that.

ACTING CHAIR MODLIN: Right.

DR. SELF: So then you should be able to give some sense of the absolute rates of those safety events. Right? What would those be? They're probably in the table somewhere but could you just --

DR. CONNOR: It just depends on what you believe about whether TIV causes any of those events or those events are basically

placebo events for wheezing and hospitalization. We don't have the same duration. So I can't estimate what those would be against placebo from these other trials.

ACTING CHAIR MODLIN: Other questions? Phil.

DR. LaRUSSA: Yes, just one other clarification about Slide 48. Hospitalizations are hospitalizations due to wheezing or asthma or any hospitalization?

DR. CONNOR: No, they're any hospitalization. The measure -- The only time that I was talking about hospitalizations for wheezing and asthma are to those two slides about severity. Those are within the wheezing and asthma population. Everybody else, this is all-cause hospitalizations and as I showed you, we're a little puzzled by the hospitalization outcomes frankly which is why we need to do additional work because many, many of those

hospitalizations are way beyond 42 days. I mean the distribution is really constant through the time period. So I'm having a hard time understanding the biology of that as opposed to understanding the biology of potentially a wheezing event that occurs in proximity to vaccination.

ACTING CHAIR MODLIN: Any further questions? Yes. Dr. Moulton.

DR. MOULTON: Yes. I just want to follow up on a question by Dr. Daum. I think his question also related to the international aspects of the ascertainment --

DR. CONNOR: Right.

DR. MOULTON: -- of the history of wheezing because many of those languages may or may not even have developed terms of wheezing and asthma as we know it.

DR. CONNOR: Yes. Those words. We actually specifically -- The same ascertainment was done throughout the world. All the training that was done of each of

the sites was done appropriately in the culturally-appropriate sort of manner and all the ascertainment that was done in terms of monitoring of records and things were all done by native language-speaking folks in those countries.

ACTING CHAIR MODLIN: Other questions? Ed, could I ask? Obviously, the risk/benefit analysis in Slide 48 is critical, but you have done that -- have excluded the children who did have a history of wheezing in this trial. What if you do the same analysis in the trial data with including all the kids including those who had a history of wheezing? I think it would be critically important because even though the label may exclude these kids as we all know, there's certainly a possibility that a number of these kids could receive vaccine.

DR. CONNOR: Yes John, we do have the analyses for the opposite group of kids, the kids with the history of wheezing and I

can -- Why don't you show this first, Chris, which is the whole population. Now this is these 12 to 23 month olds, not the entire population because we didn't see any issue above 23. But this is what the regardless of history of wheezing looks like for 12 to 23 month old kids for 180 days and then I think we actually also have the opposite. We have the kids with the history which we can bring up in just a minute.

So we have some data. We'll show you these when the slides come up and then the other question that we've grappled with is assuming that the indication is the indication and the ascertainments in the real world is not perfect compared to the ascertainment in the trial. What happens is various errors get made in one direction or another and at some point, we can go over that stuff with you also. But this is the -- These are the data for 12 to 23 and 24 to 59 in the kids with the history of wheezing.

So presumably if a child moved from the other category into this category, this would define their risks. Obviously, in the younger age group and in this population as a whole, the confidence intervals are much wider because this is a smaller group of kids.

ACTING CHAIR MODLIN: That's important but it seems to me the slide that you just showed is the real relevant one which is the entire population which would be the most likely to be a real world type of situation.

DR. CONNOR: Right.

ACTING CHAIR MODLIN: Are there other -- Yes, Bruce.

DR. GELLIN: You've provided data on somewhat historical events. The question is with an ongoing use of FluMist in the children in these studies who have had multiple doses over years, do you have any information on them particularly from a

safety perspective if they get it every year for three or four years?

DR. CONNOR: We haven't collected -- Certainly from a reactogenicity perspective, reactogenicity rates go down with the second dose and with subsequent years. There were no in the trials that were done that were sequential trials, but we didn't see any signals in those trials in the first year. So saying that we didn't see any in the second year doesn't really help that much and most of these trials were not done sequentially. Paul Glezen and others have done multiple years of vaccination and at some point if Paul is here, he may want to comment on his ongoing community-based trials related to asthma and wheezing too.

ACTING CHAIR MODLIN: I saw Paul out in the hall. Is he here? Maybe he's still out in the hall.

DR. CONNOR: No. There he is.

ACTING CHAIR MODLIN: The

question, Paul, was safety of repeated doses. Is that right, Bruce? Yes. Paul, we need to ask you to state your name even though we all know you.

DR. GLEZEN: Paul Glezen from Baylor College of Medicine. Tony Piedra has published our data on sequential doses and essentially the risk of any sort of adverse event goes down with subsequent doses. So we have data published up to four years of consecutive doses and in this age group also. I'm going to make a presentation during public comments. So I'll add a little detail to that. Thank you.

ACTING CHAIR MODLIN: If there are no further questions, we'll take a break and the agenda means that we're supposed to be back at 10:15 a.m. sharp. We'll try to stick to that.

(Whereupon, at 10:08 a.m., the above-entitled matter recessed and reconvened at 10:20 a.m. the same day.)

ACTING CHAIR MODLIN: I believe that Dr. Cvetkovich will be leading the presentation. Is that correct? Yes. Terrific.

DR. CVETKOVICH: Good morning. I'm Therese Cvetkovich, Medical Officer in the Division of Vaccines. For the FDA presentation, this is the supplemental BLA submitted to FDA in June of 2006. It has a ten-month clock. MedImmune, the Applicant, is seeking to extend the indication for FluMist to those one year to 59 months of age.

The FDA presentation will consist of presentation of the efficacy data by me, followed by presentation of the safety data by Dr. Melisse Baylor and presentation of the statistical perspective by Dr. Sang Ahnn.

Studies you see outlined here provided the majority of the data submitted by the Applicant to support the safety and efficacy of FluMist in children less than 59

months of age. Since they've already been fairly clearly described, I won't go through them again here. Just to point out, included in the supplement were data from Study AV018 which was data on concurrent administration of MMR and V with FluMist and we're not going to go ahead -- we're not going to discuss those today, but I thought I would just make the point that those were included.

As you've heard, MICP111 was a large phase three, double-blinded evaluation of the safety and efficacy of FluMist compared to TIV in children six to 59 months of age. The study enrollment was stratified by age, first of all, six to 23 months and 24 to 59 months, and this was done to ensure that there was adequate power in the six to 23 month old age strata to allow efficacy to be evaluated. At the time the study was initiated, yearly influenza vaccination was recommended for this age group only.

The older age group was further

stratified by TIV dosing recommendations into those 24 to 35 months of age and 36 to 59 months of age based on TIV dosing recommendations. Additional stratification factors included prior influenza vaccination as we've already heard that created two groups, those receiving a single dose and those receiving two doses as well as country or geographic area and wheezing history as defined by the protocol and these definitions for safety will be more fully described in Dr. Melisse Baylor's presentation.

I know Dr. Connor went through these already. I'll just mention as far as different definitions that were in the protocol, again, the primary endpoint as you see it, the relative efficacy of FluMist compared to TIV against culture confirmed influenza illness. Influenza illness is then further described as being culture confirmed, modified CDC-ILI. Antigenically similar, wild-type strains acquired in the community

and when we're talking about antigenically similar, it's to those contained in the vaccine for that year and which occurred during the influenza surveillance period and at least 14 days after the last required vaccination.

Modified CDC-ILI, we already described. Only to note that runny nose, nasal congestion was also included in case that would capture a few more children.

I have outlined here the qualifying symptoms for obtaining a nasal swab during the influenza surveillance period, one of these symptoms, and I think you can see fever, wheezing, shortness of breath, pneumonia, otitis media or two of these more or somewhat less specific symptoms here. I think it's worthy of noting although I took the number of swabs out of presentation on a slide, but there were more than 20,000 swabs collected over the influenza surveillance period to end up

identifying three to four percent of those being positive for flu, so a lot of work.

These were the analysis population. Of course, the intent to treat included all randomized subjects and then as-treated population was derived from the intent to treat population and it included randomized subjects who had at least one surveillance contact, didn't have a major protocol violation and was analyzed according to the active vaccination received at dose one. And again, the definition of the major protocol violation was one likely to affect the clinical observations or response to vaccination of the subject.

Let's see if I got rid of the table or not. So in going over the results, again just to note that 49 percent of subjects were enrolled in the U.S. and 45 percent in Europe and the Middle East with a small contribution from sites in Asia, conducted in 2004-2005 and we already

discussed the two different dosing groups.

These are just some of the baseline population demographics and I think as I already described these were generally well balanced across the two study groups and I guess just to note that there were 22 percent in this prior flu vaccination group, six percent with protocol-defined wheezing and small numbers of nonwhite and Hispanic children enrolled so that when you go to look at efficacy or other analyses for evaluation of consistency of affected, numbers in those subgroups they're really fairly small.

And again, just to show you that to get to the ATP population which was about 3900 kids in each group, exclusion from the ITT population was mainly based on the children receiving the incorrect number of doses and somewhat more of those in the FluMist than in the TIV group.

I have this up here just to mention one issue that came up during the

conduct of the study and that was that in the 0.25 mL dose of TIV which is recommended, of course, for use in six to 35 month olds was available only in the U.S. and Asia and that availability or lack of availability in the European sites, therefore restricted enrollment in the U.S., mainly in the U.S. and Asia to children six to 35 months of age.

And I hope you can see this a little better than I can. This is the analysis of the primary endpoint of MICP111. Again, these are positive influenza cultures in children with appropriate disease or influenza disease and these are all antigenically related strains. So in looking at the overall analysis, on the left here you have the influenza strain whether antigenically related or unrelated and then each of the two groups. This is the absolute difference between the two groups, relative efficacy and then the 95 percent confidence interval over here.

And as you can see, for antigenically related strains, we did have -- There was some A/H1 with a rate of 0.1 in the FluMist group and 0.7 in the TIV group. I can hardly see it. The relative efficacy was 45 percent and you can see the 95 percent confidence interval here. B antigenically similar also circulated with rates a little bit closer together. In the FluMist, 1.3 versus 1.7 in the TIV group and you can see that there was somewhat less efficacy for the B strain versus the A and that's how you ended up with this in-between relative efficacy for the overall analysis of antigenically similar strains.

This shows the analysis of the same endpoint but looking at the antigenically dissimilar strains circulated in that year. Same setup as before. Here you see all of the A/H1 for that year was antigenically similar. A/H3, there was quite a bit of this antigenically dissimilar

circulating and again a dissimilar B was circulating. So you can see that for this unrelated A/H3 strain the absolute difference was 3.6 percent, relative efficacy 79 and this is the 95 percent confidence interval and then the other strain that made up this analysis, of course, was the B strain with fairly similar number of cases in both groups and relative efficacy of six and again you see the 95 percent confidence interval here.

This is an analysis that just combines -- that represents all strains, all wild-type strains, that were detected during the conduct of the study and which met all of the definitions. So it was antigenically similar and dissimilar and I guess I would just point out that overall the absolute difference between the two groups was 4.7 percent, relative efficacy of 55 percent with a 95 percent confidence interval of 45. And I think that's 63.

Again, as Dr. Connor already

discussed, efficacy was evaluated in all of the prespecified subgroups and I won't go into this in any detail. It's difficult to see. Some of the numbers in the subgroups are really too small to make very much of. Gender was well balanced and seemed to be consistent with the overall results and again the numbers of the different races or ethnicities were really fairly small as was protocol-defined wheezing history.

Of interest, this is presentation of the primary endpoint analyzed in the U.S. population and I just want to point out that again this was a little bit different in that only children six to 35 months were enrolled in the U.S. So they basically reflected the influenza season going on in the U.S. On the left side, we have the strain. This is similar, antigenically similar, antigenically different and all combined, FluMist again and TIV and the same analysis over here. You can see that in the U.S. looking at only

antigenically similar strains there was no A/H1 and no A/H3. So that in effect, the analysis of antigenically similar strains in kids that were six to 35 months is represented here with an absolute difference of rate of 0.6 percent, relative efficacy of 35 and this is a 95 percent confidence interval.

You do pick up the antigenically dissimilar A/H3 that was circulating and the efficacy against that showed a rate difference, actually I don't have that, but it was 0.6 in the FluMist group versus 4.4. The other strain that circulated that was dissimilar was a B strain and again you have rates that are very similar in the two groups, 0.9 and 0.8, and the overall efficacy for the antigenically dissimilar strains was 68 with the 95 percent confidence interval here of 53 and 79 and, of course, this just represents these three strains combined.

So just to point out that in

looking at the prespecified age subgroups six to 23 months and 24 to 59, again because all of these six to 23 month olds were enrolled in the U.S. Their results, of course, reflect the epidemic in that year. So when looking at antigenically similar strains, you could have some concern about this relative efficacy of 29 which crosses zero. Looking at antigenically similar, however, you see that the difference is 3.4 percent, 64 percent relative efficacy and in looking at all strains combined, again you have an absolute difference of four percent and a relative efficacy of 56 percent which looks very similar to what we're seeing when looking at the 24 to 59 month olds in which efficacy was 54 percent with a confidence interval of 42 and 65.

So to conclude for MICP111 in looking at efficacy, clearly it was a large, adequate and well controlled study that looked at the relative efficacy using an

active control TIV. It was conducted at multiple geographic sites which was a strength in that it allowed many of the worldwide circulating strains to be picked up, have the objective clinical endpoint of culture-confirmed CDC-ILI. We saw efficacy against A strains both similar and dissimilar, 79 percent and 89 percent. Again for the B strains, similar and dissimilar, overall efficacy was about 16 percent and again the study had adequate power in both of the prespecified age subgroups.

Now I'd like to go fairly quickly over the other three studies, D153/P501 and AV006. Again, D153/P501 again a phase three study, randomized three to two and it was a double-blinded comparison to placebo. It was conducted in about 2700 healthy 12 to 36 month old children in Asia the years 2000-2003. The primary endpoint again was cultural confirmed ILI during the first influenza season and I'm only going to

present data for this first season.

So this is the analysis of the primary endpoint. You have both A strains antigenically similar represented here with 81 and 90 percent efficacy and a B strain that was antigenically similar with a 44 percent efficacy. So looking at all strains for the primary endpoint, the absolute difference between FluMist and placebo was 9.1 percent, efficacy was 73 percent and the 95 percent confidence interval 63 and 81.

This slide just represents all strains so that would include both antigenically similar and dissimilar so that you're picking up some A/H3 and also antigenically dissimilar B. Overall, the absolute efficacy was 70 percent in looking at strains combined.

AV006 you've heard about, a phase three study, randomized two to one with a placebo control that was conducted over two years. In this study about 1600 children, 15

to 71 months of age were enrolled and the primary endpoint again was culture-confirmed influenza illness due to antigenically similar strains, antigenically similar to those contained in the vaccine.

These are the efficacy results for Year one, FluMist and placebo. No H1 circulated in that year. So we have here the antigenically similar A/H3 and B. The rate in the FluMist group was 0.7 for both and the rate in the placebo group was 12 and 7 and the efficacy was 95 and 91 so that for this B strain, it looks like it's doing a little better, those strains identified or cultured during the years this was conducted, `97-`98, etc. It looks like it's doing a little better than the more current circulating strains. But the overall efficacy was 93 percent.

In Year two, this was driven -- Efficacy results were driven mainly by this A strain which was an antigenically dissimilar

strain to that contained in that year's vaccine. There were a few other B strains that were antigenically similar that were picked up here, but overall the efficacy for that year based mainly on results in this dissimilar strain was 86 percent and you have your 95 percent confidence interval.

So in summarizing these two studies as well as the summary from D153/P501 or MICP111, both studies were adequate and well controlled phase three studies that evaluated objective clinical endpoints. You had FluMist compared to placebo in these two studies and compared to TIV and MICP111 and again you had efficacy demonstrated for both antigenically similar and dissimilar A strains in AV006 and also for B.

Overall, our efficacy conclusions are that efficacy for FluMist has been demonstrated against culture confirmed ILI. We have at least three full years of data and for some studies, an additional year and

these data represent different community acquired influenza strains both antigenically similar and antigenically dissimilar to those contained in the vaccine.

Now I want to introduce Dr. Melisse Baylor who will present the safety analysis.

DR. BAYLOR: Hi. My name is Melisse Baylor and I'll discuss the FDA clinical analysis of safety. I plan to discuss safety data from the three main studies in the supplemental BLA, studies MICP111, D153/P501 and AV006.

For study MICP111, I'll cover reactogenicity events, adverse events, new medical diagnosis, new medical conditions diagnosed during follow-ups, serious adverse events, death and then data on wheezing and hospitalizations. I'll discuss the other two studies much more briefly.

I know that you've heard a lot today already about study MICP111, but I do

want to remind you of the entry criteria. Children were excluded for a history of severe asthma, for wheezing diagnosed by a health care provider in the previous 42 days or for bronchodilator use or steroid use in the previous 42 days. Severe asthma in the inclusion criteria was defined by using the NHLBI guidelines, asthma exacerbations that require inhaled beta-2 agonist more often than every four hours over a 24 hour period with episodes that occur less than six weeks apart.

In MICP111, the parents and guardians were given a diary card and were specifically asked to record whether or not subjects had any of the symptoms listed here as a reactogenicity event. Let me see. Parents or guardians were also asked to take and record the child's temperature every day. Adverse events other than those specifically asked about were called just that, adverse events and information on medically

significant wheezing which was discussed already by the Applicant, reactogenicity events and adverse events were collected for the 42 days after the last study vaccine. Serious adverse events and significant new medical conditions were followed for the entire study period.

The Applicant reviewed reactogenicity events, but I would just like to highlight a few things. First overall, reactogenicity events were reported more frequently in the FluMist arm, 69 percent compared to 63 percent after the first dose. There were fewer reactogenicity events after the second dose of study vaccine but the frequency of reactogenicity events was again higher in FluMist recipients.

In the FluMist arm, there was an increase runny, stuffy nose and low grade fever. In the subgroup of children that were less than 24 months of age, there was an overall higher frequency of reactogenicity

events in the FluMist group, 75 percent versus 67 percent in the TIV arm. Cough was also more common in the younger children and was seen slightly more often in FluMist recipients.

I know the Applicant has also discussed adverse events and I'll quickly just point out that the largest difference between FluMist and the TIV arms when the rate was actually higher in the FluMist arm was sneezing and that rate difference was only 1.1 percent.

Finally, significant new medical conditions were defined as any diagnosis of a new chronic illness during the entire 180 day follow-up period. In this table, conditions are shown if they occurred in at least two persons in either treatment arm. As you can see in the table, the most common new condition in both arms was asthma and asthma was slightly more common in FluMist recipients.

Again, as the Applicant discussed, there were two deaths. Both were accidental and neither was related to the study vaccine and then as you can see in the bottom part of this slide, regardless of the time cutoff used from 10 to 180 days the percentage of subjects with SAEs was similar between the two study arms.

Serious adverse events in the first six weeks are shown in this table and as you can see, most of the SAEs were typical illnesses that are seen in childhood particularly in the winter months when this study was conducted. Although the number of subjects with serious events were very small, pneumonia was the most common SAE and it was reported in 15 FluMist recipients compared to 10 TIV recipients.

Next I'd like to move onto wheezing and information on wheezing was collected several different ways. It was collected as a reactogenicity event, as an

adverse event and as a medically-significant wheezing. The definition of MSW was explained by the Applicant. It's wheezing on exam plus a sign of respiratory distress, hypoxemia or new prescription for a daily bronchodilator. And MSW was the primary definition used by the Applicant in their safety analysis. However, the clinical team reviewing safety preferred to analyze wheezing using one of the secondary endpoints in the study and that is what we called all wheezing which included the preferred terms or adverse event terms for asthma, bronchiolitis, brochospasm and the symptom of wheezing. This allowed us to look at all subjects with wheezing and not just a subgroup of subjects with wheezing. But MSW was analyzed by the FDA statistical reviewer and will be discussed next by Dr. Ahnn.

Before we get into the actual data discussion of wheezing, I wanted to point out the two different definitions used to define

history of wheezing. The protocol definition of wheezing was a history of wheezing of three or more wheezing events that required medical attention. Any wheezing history was defined as wheezing by either the parent/guardian history or by the medical record or both. And as you can see, there were fewer subjects with protocol history of wheezing which is not surprising in a study that was enrolling infants down to six months of age who hadn't had a whole lot of time to have three wheezing events.

This table shows an analysis of subjects with any of the four all wheezing events during the 42 days following vaccination and I'll work my way down the table. As you can see, seven percent of subjects in the FluMist arm and six percent in the TIV arm had a wheezing event during the study. The gender breakdown was similar with slightly more than 50 percent of males in each study arm.

The majority of subjects in this study who had wheezing were white, 76 percent and 81 percent, and the majority of subjects in the whole study were white, about 80 percent. So this is consistent with the composition of the study. As you can see, there does appear to be an imbalance in blacks and Hispanics in this analysis. However the number of blacks and Hispanics in the entire study was relatively low and when you look at rate differences for these which weren't put up, there was only a two percent rate difference here and a three percent rate difference here. So in reality, the rate differences were not much.

The average age was slightly younger in the FluMist arm at 20 months and 22 months in the TIV arm and if you look, only 17 percent of subjects with wheezing had a history of wheezing using the protocol definition. But of subjects who had any history of wheezing whether it be by their

parent or by their medical record, it was 41 to 45 percent.

Finally, a larger percentage of subjects in the FluMist arm didn't receive their second dose of study vaccine compared to those in the TIV arm. So you have 11 percent versus 7.5 percent.

Now this slide changes the perspective a little bit because we're looking at all wheezing events by events instead of looking at it by subjects and you can see there were slightly more events in the FluMist arm compared to the TIV arm. Asthma was diagnosed more often in the FluMist arm compared to the TIV arm and the more symptomatic and descriptive term of wheezing was diagnosed more in the TIV arm than in the FluMist arm.

Approximately 58 percent of the wheezing events occurred after dose one and the time of onset was similar between the two arms and finally in severity there were more

moderate and more severe, and those are highlighted, of wheezing events in the FluMist arm compared to the TIV arm, but no difference in hospitalization.

As you can see on this slide, wheezing events were relatively uncommon in the first ten days after vaccination and similar between the two arms. And most wheezing events were observed more than 42 days or six weeks after vaccination. The only difference between the two arms was minor and is the slight increase in events seen in the 11 to 21 day period and that's higher in the FluMist than in the TIV arm.

Duration of wheezing is shown in this slide. And the duration of wheezing was similar between the two arms for bronchiolitis, bronchospasm and wheezing, but not for asthma. It turns out that the term "asthma" actually has three kind of subterms for it, acute asthma, asthma exacerbation and persistent cough due to asthma and the

difference in duration in asthma is all driven by the persistent cough that these children have. Some had persistent cough up to 180 days, basically to the end of follow-up period.

Next, I want to address wheezing by age and as you've heard, the study enrolled subjects six to 59 months of age and the Applicant has proposed limiting the indication to 12 months of age and older. So in my analysis of age, I looked at the age groups six to eleven months, 12 to 23 months, 24 to 35 months and 36 months and older even though doing the six to 11 months and 12 to 23 months splits up a prespecified age group and you end up with two smaller age groups that weren't properly randomized.

As you can see in this analysis, the majority of subjects with wheezing events were less than 24 months of age in the shaded boxes. In the FluMist arm, the age subgroup, this age group of less than 24 months of age,

right here, had the greatest percentage of subjects with wheezing and it made up about two-thirds of the wheezing subjects in the FluMist arm.

Now there was a greater percentage of all study subjects in the same age subgroup with wheezing in children less than 24 months of age in the FluMist arm compared to the TIV arm. So you see 11 percent, let me see, 11 percent of six to 11 month olds who received FluMist had a wheezing event compared to nine percent of children six to 11 months old who had received TIV. In addition, nine percent of 12 to 23 month olds who received FluMist had a wheezing event compared to six percent with a wheezing event in subjects who had TIV.

As far as severity of wheezing, there were more severe events in the 42 days post vaccination in the FluMist arm than in the TIV arm for children less than 24 months of age and you see here, it's ten versus

three and there are more events resulting in hospitalization and that's seven versus four and more subjects that did not receive their second dose of vaccine which is 23 versus 12. Although the numbers are small, they're consistent in each analysis and they're consistent in the two subgroups of age and they are not observed in children older than 24 months of age.

Here are the number of serious all wheezing events during the study and as you can see, there were very few serious all wheezing events, nine in the FluMist arm compared to six in the TIV arm and again, it's a small but consistent difference between the two arms.

Additional analyses that I briefly wanted to address are included here. An analysis by gender, there were more wheezing events in males than in females which is consistent with what's typically seen in pediatrics. Eighty percent of the study

population was white. So it was difficult to determine any differences by race, but none were observed and there was little difference in wheezing by what country the subject was enrolled in.

Finally, I analyzed what other upper and lower respiratory adverse events were reported in subjects with wheezing events and there was an increased number of events of pulmonary congestion and of sinusitis in the FluMist arm. The good news is that there were very few events of respiratory distress, hypoxia and tachypnea reported in the entire study and they were in both groups. So they were balanced.

The Applicant has also proposed limiting FluMist to subjects without a history of wheezing. So the next several slides look at subjects with and without a history of wheezing. This slide includes subjects in the FluMist arm only and compares subjects who receive FluMist and had a

wheezing event by their history of wheezing. So those in the first column right here had a history of wheezing and had a wheezing event post FluMist and those in the second column had no history of wheezing but had a wheezing event after receiving FluMist in the study. And I used history of any wheezing because this would be the definition that would be used in the real world after licensure.

And as you can see in this analysis, bronchiolitis which is a viral infection, the results in wheezing was more common in children without a history of wheezing while just the symptom of wheezing was more common in children with a positive history of wheezing. But the main purpose and the reason I did this analysis was to examine the influence of history of wheezing on the severity of wheezing and that means I wanted to see if wheezing after FluMist in subjects with a history of wheezing was any

worse than wheezing in subjects who had never wheezed before and it was not. As you can see the number of severe events, the number of subjects hospitalized and the number of subjects who did not get their second dose was similar whether or not the subject had a history of wheezing.

Because the Applicant has also proposed limiting the indication for FluMist to children 12 months and up, I looked at the same information as shown on the last slide, but this time by age subgroups. So this again compares wheezing events in the FluMist arm by a history of wheezing or not wheezing and now adds age subgroups to the mix. As you can see in these two shaded areas right here, severity is measured by number of severe events, number of subjects hospitalized and number of children not receiving their second dose of FluMist was higher overall for subjects less than 24 months of age compared to the older children

over 24 months of age. Now when you're comparing within this stated area, the positive history and negative history in children less than 24 months of age, the severity was similar except for fewer children with a history of wheezing got their second dose of FluMist.

Now if you look at the next two columns here in the 24 to 35 month age range, you'll see there was an increase in moderate and severe events with a history of wheezing. However, there was no increase in the number of subjects hospitalized and there was no increase in the number of subjects who did not receive dose two. So overall, it does not appear that subjects regardless of their age who have a history of wheezing had more severe wheezing post vaccination with FluMist.

Next, I wanted to change the focus a little and I looked at the predictive value of the history of wheezing. In this

analysis, I looked at the study subjects who had a history of wheezing on entering the study and I used both the protocol definition -- I'm sorry. I used any history definition and I analyzed how many subjects with a history of wheezing actually had a wheezing event and how many subjects without a history of wheezing had a wheezing event after receiving the study vaccine. And you can see the history of wheezing regardless of the treatment group was not very useful in predicting a wheezing event in the 42 days after vaccination with FluMist or with TIV.

This slide shows the same analysis as that slide, but by age cohort to see if there is a history of wheezing or not, is more helpful at predicting wheezing post vaccination in any particular age group. In this slide, I used the history of wheezing of any wheezing again and as you can see, more children with a history of wheezing had wheezing after receiving FluMist in the six

to 23 month age cohort which is 23 percent here compared to subjects in the six to 23 month age cohort for TIV or the older children who received FluMist or TIV and all the other results for positive history are less than 11 percent. However, only 23 percent of those with a history of wheezing post vaccination in this cohort. So even at its best, the 23 percent, a history of wheezing was not very predictive of wheezing post vaccination.

Now I want to switch to a discussion of hospitalization. In the Applicant's presentation, they explained that they proposed limiting indication to children 12 months of age and older because of the increase in hospitalizations observed in children six to 11 months of age as shown in the data on this slide.

The next three slides will show the Applicant's analysis of hospitalization by age and by history of wheezing. They also

divided hospitalizations in all-cause hospitalization and respiratory hospitalization. And as you can see in this slide and I think the Applicant pointed out, there was an increase in all-cause hospitalizations and in respiratory hospitalizations regardless of wheezing history in patients that were six to 11 months of age.

Now here's the same slide but with the subgroup of children 12 to 23 months of age highlighted here and in this subgroup, there was an increase in both all-cause and in respiratory hospitalizations in the FluMist group, but only for those subjects with a positive history of wheezing.

Finally, here's the same slide a third time but this time it has the oldest group highlighted, those over 24 months of age and this subgroup there was little influence of history of wheezing on hospitalization and the rates of

hospitalization were either similar to or actually higher in the TIV arm. So again, there seems to be a cut point at 24 months.

I further analyzed hospitalization by age for those with respiratory events. I know you saw respiratory hospitalizations in the last slide, but I used a different definition of respiratory events than the Applicant and in my analysis, I limited respiratory events to those that were more acute and to those that occurred within 42 days of vaccination. So I didn't include some of the more chronic respiratory events that were included in the Applicant's definition of respiratory hospitalizations such as tonsillar hypertrophy, adenoidal disorder, etc. And as you can see, there was a greater percentage of subjects less than 24 months of age with respiratory hospitalizations in the FluMist arm compared to the TIV arm and that was not seen in children older than 24 months of age.

Finally, I looked at hospitalizations in the first two weeks post vaccination to examine events that had a closer temporal relationship to vaccination. Most of the hospitalizations were for typical childhood illnesses. But as you can see, the only real difference between the two arms was the increase in pneumonia that was noted in the FluMist arm where you have nine cases compared to three cases in the TIV arm and the majority of pneumonia events were in subjects less than 24 months of age.

In this bar graph, the number of hospitalizations by month of age, it shows the number of hospitalizations by month of age. Now the CAIV-T is FluMist. It's red and TIV is green. It's very Christmasy slide in spite of the fact that it's May and what I wanted to show on this slide is and it's similar to one shown by the Applicant is to show the dangers of post hoc analysis subgroup analysis so that you can see the

majority of differences are early. But there are some late differences also and the results would have varied depending on where you decide to make your cut and if you made your cut like at 13 months, the result would be different. But it also may be different if you made it here. So it's very dangerous to just start to go playing within prestratified age subgroups.

Now I'd like to turn the focus to pneumonia events and just two slides ago, I showed an analysis of hospitalizations in the two weeks vaccination and there was more pneumonia in the FluMist arm than in the TIV arm and the results on this slide show that the overall number of pneumonia events and number of subjects with pneumonia was similar between the two treatment arms, but there were more subjects with moderate and severe pneumonia in the FluMist arm. Let me see if I can find the pointer and there were more subjects who were hospitalized in the FluMist

arm than in the TIV arm.

In response to the Applicant's analysis by age, I also looked at age subgroups for pneumonia and in this analysis, pneumonia was more common in children less than 24 months in both age groups and it was more common in the FluMist arm than in the TIV arm with 38 cases compared to 29. But you see the signal is not seen in children 24 months of age and older.

Finally, I analyzed safety results from the two placebo control trials. In study AV006, the placebo was the vehicle or allantoic fluid. And this study enrolled children 15 to 71 months of age and excluded those with a history of wheezing or bronchodilator use in the previous three months. Although my review of the study was limited due to the lack of adverse event datasets, there was no increase in respiratory events or in asthma in FluMist recipients noted by the Applicant.

Hospitalizations were uncommon and they were reported in less than one percent of subjects in either arm.

Next, children from 12 to 35 months of age with no wheezing the previous two weeks were enrolled in study D153/P501 and the placebo used in this study was normal saline. In this study, the safety results are limited by the short 11 day follow-up time and there was no increase noted. But in this 11 days, there was no increase noted in bronchospasm, bronchiolitis or pneumonia or in the number of hospitalizations in FluMist recipients.

So in summary, although FluMist appeared to be safe and effective in children 24 months of age and older, there were safety concerns in children less than 24 months of age. These are mainly in study MICP111 which provides the majority of support for this application and in this age group of children less than 24 months, there was a small but

consistent increase in the number of hospitalizations, the severity of wheezing, the severity of respiratory events such as pneumonia and finally, a history of wheezing was poorly predictive of wheezing post vaccination.

I'd like to introduce Dr. Ahnn, our statistician, who will present his findings.

DR. AHNN: Hi. My name is Sang Ahnn. I'm a CBER biostatistician for this product. I focused my presentation on the safety issues in MICP111 which is the main study for this licensure.

I have to repeat briefly the design of this study which was already said two or three times by the Applicant and the CBER clinical review. So NICP111 is a multi-center, double-blind, randomized study to compare the clinical efficacy and safety of FluMist when it is compared to TIV. About 8500 subjects were randomized either to

FluMist or TIV in a one to one ratio stratified by age, prior influenza vaccination status and wheezing history status which is greater than or equal to three wheezing illnesses requiring medical follow-up or hospitalization and countries. So those are the four prespecified strata for the randomization.

MICP111 was performed in children six to 59 months of age including those with a history of wheezing or asthma, but children with medically-diagnosed or treated wheezing within 42 days before enrollment or with history of severe asthma were excluded. That was the exclusion criteria for this study.

The Applicant is seeking indication extension of FluMist for children up to 59 months of age excluding those children with a history of wheezing or asthma. So that's the sponsor's sought indication to up 59 month excluding those children with a history of wheezing or

asthma.

Okay. Wheezing history variables were used in three different ways. First, it was used as a exclusion criteria. Subjects with medically-diagnosed or treated wheezing within 42 days before enrollment or with history of severe asthma were excluded from the study as an exclusion criteria and it was also used as a stratum for randomization. Subjects with greater than or equal to three wheezing illnesses requiring medical follow-up or hospitalization is a prespecified subgroup within which subjects were randomized. Also wheezing history was used as a post hoc subgroup. So a subject with any history of wheezing is a post hoc, nonrandomized subgroup which is used for analysis and the Applicant's sought indication.

This is the results for medically-significant wheezing. Medically-significant wheezing is the prespecified safety endpoint

of primary concern and the definition, I think it was already said two or three times, but I have to repeat it just one more time. Medically-significant wheezing was defined as the presence of wheezing on physical examination plus at least one of the following: sign of respiratory distress or hypoxia or to saturation less than 95 percent or new prescription for daily bronchodilator therapy not as needed basis. So an observation period for this safety endpoint is 42 days after vaccination, after the last dose.

So this is -- The first row of this table is the whole group result. So six to 59 months of the whole study population, the attack rate of medically-significant wheezing in FluMist group is 3.9 percent versus attack rate of medically-significant wheezing in the comparative group, TIV group, is 3.1 and the relative risk is 1.24. So that's the results for the whole study

population. Especially in the six to 23 month strata, the attack rate of medically-significant wheezing in FluMist is about six percent versus about four percent in TIV group and the relative risk in this age strata six to 23 months is 1.55 and lower bound of the 95 confidence interval is 1.17.

The next slide is on the medically-significant wheezing related hospitalization. The definition of medically-significant wheezing related hospitalization is you first have to have the medically-significant wheezing within 42 days after vaccination. Once you have the medically-significant wheezing event, you have to be hospitalization within seven days after that incident. So that's the definition of medically-significant wheezing related hospitalization. Of course, this study is not powered to detect the difference between the hospitalization rate. The hospitalization is usually so late, so rare.

So the first row of this table is the whole study population and attack rate of medically-significant wheezing related hospitalization in FluMist group is about 0.3 percent versus 0.2 percent. The number is 12 hospitalization in FluMist group versus eight hospitalization in TIV group as a whole. Especially six to 23 month strata, the number of hospitalization in the FluMist is ten versus four in TIV and the relative risk is 2.48, but this study is not powered again to detect the actual difference.

Here exclusion of six to 11 month old from the sought indication, the Applicant stated that in children six to 11 months of age rates of medically-significant wheezing and rates of hospitalization were higher in FluMist than it is compared to TIV group. This result is the basis for Applicant excluding six to 11 months subgroup from the sought indication.

Here I further break this six to

23 month age strata into two subgroups, six to 11 months and 12 to 23 months. Okay. Six to 23 months we already saw the significant increase in terms of medically-significantly increased risk in terms of medically-significant wheezing. If you break down this age strata into two, see here six to 11 months subgroup, you still see the increased risk. But also in 12 to 23 months group, you also see the increased risk here and it's statistically significant. So this is based on medically-significant wheezing.

Now the next slide is based on medically-significant wheezing related hospitalization. So six to 23 months group it was number of hospitalization is 10 versus four and relative risk is about 2.5. In six to 11 month age group, the number is four versus two and relative risk is two. Twelve to 23 months group the number is six versus two and relative risk is about three here, but it doesn't carry any statistical

significance due to the size of this study and due to the size of this subgroup too.

So per the preceding two tables you just say, in the FluMist group compared to TIV group, rates of medically-significant wheezing and rates of medically-significant wheezing related hospitalization were not only higher in the children six to 11 months of age, but also higher in those 12 to 23 months of age.

As a summary, in general, since the six to 11 month age group and also 12 to 23 months subgroup likewise is a post hoc, nonrandomized subgroup. So statistical results could be misleading due to the bias and therefore should be interpreted with caution. Specifically in terms of medically-significant wheezing and medically-significant wheezing related hospitalization, six to 11 months and 12 to 23 months subgroups show similar safety profiles. Thus, statistical rationale for just

excluding six to 11 month group from the sought indication and not excluding the entire six to 23 month group appears unclear.

This table is a little bit too busy, but the first table you already saw it before, but I just combined into two. This is the medically-significant wheezing results. The second table is after excluding the subject with history of wheezing since the sponsor's sought indication is 12 to 59 months excluding the subjects with histories of wheezing. So this is the table after excluding subjects with histories of wheezing or asthma and as you see here, there is still a safety signal in this six to 11 and 12 to 23 in terms of medically-significant wheezing, 1.32, 1.53 here.

The next table is on the medically-significant wheezing related hospitalization and the first table you already saw it. The second table is the results of medically-significant wheezing

related hospitalization after excluding subjects with the history of wheezing and it's hard to tell because the rate of medically-significant wheezing related hospitalization were so low in both of the groups, but I think you can tell from the numbers it's like three to one in six to 11 months and two to one in 12 to 23 months. But again, the six to 11 months and 12 to 23 months subgroups are post hoc and nonrandomized subgroups. So the six to 23 strata result is more reliable.

ACTING CHAIR MODLIN: Thank you, Dr. Ahnn. At this point in time, we should open up the floor for questions regarding the presentations by Dr. Cvetkovich, Dr. Baylor and Dr. Ahnn. No questions. It's heard to believe. Dr. Moulton.

DR. MOULTON: I was wondering if I could go back to the first presentation from FDA, Dr. Pratt's presentation. I had a question about some of the VAERS data. There

is a Slide No. 16 that this is clearly not directly relevant to age group. It was five to 17 years old. There were 16 asthma or wheezing events split between preexisting asthma condition seven and no preexisting conditions nine and I was just wondering, first of all, how many of these 16 were SAEs and what was the nature of the follow-up? Was that data based on just the form or were all of them contacted via telephone call? So what's the nature of the follow-up data that would have addressed the preexisting chronic condition?

DR. IZURIETA: Sorry. Can you repeat the question more slowly please?

DR. MOULTON: Okay. It's relevant to Table 16, Slide No. 16.

DR. IZURIETA: Yes. My name is Hector Izurieta from the Vaccine Safety Branch.

DR. MOULTON: Okay, and in the age group five to 17 years of the sixteen events

there, how many were severe adverse events and how many had follow-up information that is not just the form itself, but how many were contacted by telephone and actually asked about preexisting chronic conditions?

DR. IZURIETA: I don't have the numbers exactly, but approximately half of them were serious enough to have been classified as serious either hospitalization or other. Now the ones who were followed up were only those who were seen within the first two years following licensure, not those which appear afterwards which is approximately one-third of them were interviewed by telephone or the medical records were requested. So there was no intense follow-up for most of asthma cases and of course, Dr. Pratt has already reported the numerous limitations of the VAERS data analysis.

DR. MOULTON: Yes. Thank you.

ACTING CHAIR MODLIN: Dr.

Stapleton.

DR. STAPLETON: Related to that same question, do you have any data on the timing of the asthma in relationship to the FluMist?

DR. IZURIETA: Sorry.

DR. STAPLETON: Do you have any information related to the timing of the asthma occurrence in relationship to the FluMist administration?

DR. IZURIETA: In the VAERS data, most of them were within three days after vaccination.

DR. STAPLETON: Thanks.

ACTING CHAIR MODLIN: Further questions? Bob.

DR. DAUM: Thanks, John. I guess I'm harping. So I apologize for that in advance, but it strikes me that some of the most important information we've seen goes to the occurrence of medically-significant wheezing after receiving FluMist and I'm

mindful of the definition that was provided for medically-significant wheezing and hypoxia is fairly easy to quantify. Respiratory distress I think is a reasonable thing to ask physicians to agree on and I'm a little nervous about the prescription for a daily use of bronchodilator in particular as this is an international study and I'm wondering whether we can be provided with information that goes to the conclusion about the occurrence of medically-significant wheezing after the vaccines. And it's polypronged question, but one is does this difference hold up if U.S. and non U.S. subjects are analyzed and do we know anything about the prescription practices to manage asthma in the many countries that the study was done in beside the U.S. because I'm just worried that we could be not quite sure what we were looking at here unless we hear that kind of analysis.

ACTING CHAIR MODLIN: Dr. Baylor.

DR. BAYLOR: Hi. I'm Melisse Baylor. I have two kind of responses I think to your question and one is the problems with the definition of MSW, of medically-significant wheezing and the clinic team had some issues with it because it's a subgroup and it doesn't include all wheezers. So you can't -- You don't capture everybody and we felt they were left out. So that's why we used wheezing events and that's why we -- That's one of the problems we had and that's why we decided to use all wheezing events.

The second question you asked is severity or problems in the U.S. compared to non U.S. and I think that -- Well, I looked at that, the frequency in the rate of events and the severity by country and I did analysis and I can tell you what showed up is it was all very similar, but the only thing that showed up was there was an increase in wheezing in Iceland probably related to the fact that they only enrolled ten children and

it's cold there and there was an increase in hospitalizations in Hong Kong and I feel like that's probably related to the health care system in Hong Kong. But other than that, there was no difference by country.

DR. CVETKOVICH: Can I respond to that?

ACTING CHAIR MODLIN: Could you go to the microphone please?

DR. CVETKOVICH: If you're asking, this is Therese Cvetkovich, specifically about any differences in bronchodilator, use of that practice, I mean I suspect that what Dr. Connor said when he said that all or the language and everything was country appropriate, I guess that would get at it somewhat. Again, there's no question that bronchodilator use as documented here is quite subjective, but nevertheless you have large randomized study that sort of balances out the overall so that any differences I think are fairly reasonable to -- not

difficult to interpret. But other than that, I don't know. And if you have any more, you can certainly explain that.

ACTING CHAIR MODLIN: Ed.

DR. CONNOR: My only other comments would be that the reason why medically-significant -- the case definition of medically-significant wheezing was created was so that we had a common definition across both of the age groups because of all the difficulties of listening to and understanding exactly what everybody calls asthma, wheezing and various iterations of that. The reason why we specified a daily bronchodilator use is because what we were trying to avoid in that definition was the mother who said somebody wheezed because it was noisy breathing or something and the kid had upper respiratory tract illness and avoid the fairly rampart use of acute bronchodilator therapy for a day or for a couple of days on an intermittent basis.

So what we trained people on, what we were really looking for, is you used a bronchodilator because you needed to cover somebody for a period of time because you thought that episode was significant enough to do that. That was the intent and I don't know that we have any evidence unless Bob Walker wants to comment about the geographic definitions other than what was just commented on except to say that across most of the places that we were doing the trial, albeit some of the Asian countries are a little different, the routine practices associated with asthma therapy for bronchodilators at least are pretty consistent. I don't know if there's anything else that you guys want to add.

ACTING CHAIR MODLIN: Dr. Farley.

DR. FARLEY: Can someone clarify the enrollment age groups? I thought I heard in the FDA presentation that the vast majority or that in the U.S. we just enrolled

six to 35 month olds and therefore, we provided the majority from the U.S. Was it dichotomous or where they overlapping or how was the enrollment done across the 16 countries?

DR. CVETKOVICH: Therese Cventkovich, FDA. Again, I think probably Medimmune can address how enrollment occurred based on the different availability of the different TIV dosage forms. Okay, but nevertheless because only the 2.5 mL dosage form was available in the U.S. those sites then, if it helps you think about it, just restricted themselves to the appropriate age group for that dose, six to 36 months. Does that --

DR. FARLEY: Right? Wrong? Can you help?

ACTING CHAIR MODLIN: I think it had more to do with availability of the lower dose in countries other than the U.S.

DR. CVETKOVICH: Correct.

ACTING CHAIR MODLIN: As I recall. Ed do you want to clarify.

DR. CVETKOVICH: Right.

DR. CONNOR: The problem at the beginning of this trial was that it was the year that Chiron's supply wasn't available and that put pressure on the TIV supply across the trial and so what was available in the U.S. was the 0.25 dose. The higher dose wasn't available. So the populations that were enrolled in the U.S. were really just purely about availability of the formulations of TIV.

ACTING CHAIR MODLIN: Dr. Jackson.

DR. JACKSON: The question for Dr. Ahnn, I believe, just regarding a clarification of the data on hospitalization. I'll give him a second to --

DR. AHNN: Which slide?

DR. JACKSON: Well, I guess Slide 13. I think that's a duplicate of an earlier one. It looks like Slides 13 and 12 are the

same. No. Yes, 13. I guess my first question is that, regarding the differentiation between the six to 11 month and 12 to 23 my understanding from the sponsor's presentation was that they were making a distinction on the basis of a perceived difference in risk for all-cause hospitalization and not for wheezing-related hospitalization. So I wondered why those data weren't presented in your presentation.

The second is when looking at wheezing hospitalization either among the prespecified age group of six to 23 months or the further broken down groups, my interpretation of the data where the confidence intervals overlap is that no difference in risk was demonstrated, that the hypothesis of no difference cannot be rejected on the basis of these data.

The last question or comment I have is I'm a little surprised to see the data presented in terms of relative risk and

not absolute risk difference and I just wondered about the rationale for that type of presentation.

DR. AHNN: So six to 10 month group is 32 versus 24 and this is the age breakdown six to 11 and 12 to 23. And the next slide is after you exclude the subject with the history of wheezing, so here 24 versus 21. If you break it down, this age group the signal disappears as was already stated by the Applicant.

DR. JACKSON: Okay. Would you show the previous slide again, please?

DR. AHNN: Next slide again.

DR. JACKSON: The previous one.

ACTING CHAIR MODLIN: The one just before this.

DR. AHNN: Previous. This is the previous one, I think. No. Yes, this is the previous one.

DR. JACKSON: Okay. The results appear quite similar to me.

ACTING CHAIR MODLIN: Did that answer your question, Dr. Jackson?

DR. AHNN: This is all-cause within 42 days.

DR. JACKSON: Well, I guess the question I had at the end of that statement I made earlier was regarding use of relative risk versus absolute risk difference and just a statement as to why the relative risk was chosen for these analyses. What the FDA's perception of the benefit of this type of presentation of data would be?

DR. AHNN: Yes. Actually, I think -- when the sponsor presenter used both, I think, absolute difference and the relative risk and in my presentation I exclusively used relative risk. But I have the table per thousand in terms of -- let's see. This is for everybody and by each age strata. So medically-significant wheezing within 42 days post vaccination, this is absolute. The rate difference per thousand. So 21 per thousand

more medically-significant wheezing in this age group and about three more per thousand, the medically-significant wheezing- related hospitalization and this is all-cause hospitalization, about four more per thousand.

If you exclude the subject with a history of wheezing or asthma, this is after you're excluding the subject with the history of wheezing or asthma. In the six to 23 month age group, about 12 more medically-significant wheezing per thousand to about two more MSW-related hospitalization per thousand, about two more all-cause hospitalization within 42 days per thousand. If you break this age strata into two, the signal in terms of all-cause hospitalization in 12 to 23 month group disappears, but that's statistically unreliable estimate because, first of all, it's a nonrandomized subgroup, second of all, because of the smaller size.

ACTING CHAIR MODLIN: Any follow-up?

DR. JACKSON: No, thank you.

ACTING CHAIR MODLIN: Okay. Great. I had a couple questions but I think I'll put them off because we're running a little behind at least until the open discussion. We do need to move on to the open public hearing and I understand, Christine, you have some boilerplate.

MS. WALSH: As part of the FDA Advisory Committee Meeting procedure, we are required to hold an open public hearing for those members of the public who are not on the agenda and would like to make a statement concerning matters pending before the Committee. Dr. Modlin, would you please read the open public hearing statement?

ACTING CHAIR MODLIN: Yes. Thanks. I have it. Thank you. Different script. Both the Food and Drug Administration and the public believe in a

transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with the sponsor, this product and, if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging or other expenses in connection with your attendance at this meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the Committee if you do not have any such financial relationships. If you choose not to address this issue of financial

relationships at the beginning of your statement, it will not preclude you from speaking. And I understand that our first speaker will be Dr. Belshe or Dr. Glezen. Okay.

Our speaker will Dr. Paul Glezen who is representing the Central Texas Field Trial sponsored by the Control of Epidemic Influenza Grant from the NIAID. Paul?

DR. GLEZEN: Hi. I'm Paul Glezen of Baylor College of Medicine. I have served as an ad hoc consultant to Medimmune, but I paid my own way to this meeting. I'm representing the Central Texas Field Trial and I've taken an extract of a manuscript now being prepared by Dr. Gaglani and Dr. Riggs and Dr. Gaglani is a pediatric infectious disease specialist at Scott & White Clinic and Mark Riggs was the biostatistician at the time of the portion of the trial that I'm going to talk about today. He's now in an academic setting.

The main objective of the Central Texas Field Trial is to determine the proportion of children vaccinated against influenza necessary to effect herd protection for the community. An open label, nonrandomized, community-based trial funded by NIAID has been conducted in Temple-Belton, Texas with single annual doses of a live, attenuated influenza vaccine administered by nasal spray. The live, attenuated vaccine was provided by Aviron initially and then Medimmune. To date, over 38,000 doses of LAIV have been administered to children in East Bell County, Texas.

For the period from 1998 to 2002 before licensure of LAIV, the vaccine was offered to Temple-Belton children 18 months to 18 years of age. Twenty-four percent or about 4500 doses of the 18,780 doses administered during that period were given to children less than five years of age. Three thousand, four hundred twenty-six of those

LAIV doses given to children 1.5 to four years of age received care at Scott & White Clinic in Temple. These Scott & White clinic patients are the subjects of this report because of the availability of medical records prior to vaccination.

Children with mild intermittent asthma or reactive airway disease were included if they met the following criteria: not allergic to eggs, not on chronic asthma treatment, no ER visit or hospitalization for RAD for the past year or the past six months for children less than two years of age. Inactivated influenza vaccine was offered to those not eligible to receive the live attenuated vaccine.

Six hundred six Scott & White children less than five years of age had a history compatible with mild intermittent asthma or reactive airway disease. The history obtained from the parent was used to determine the status at the time of

enrollment. Later, the medical records for the Scott & White children were reviewed to verify the status. About one-half of the parent histories were confirmed by medical record review, but a similar number was identified by medical record only.

To determine the relative risk of medically-attended acute respiratory illness including wheezing illness or asthma RAD, all events for the LAIV recipients were determined from the first day of the LAIV campaign until 42 days after the last day of LAIV delivery and that usually included a period of about three months. The method of analysis was suggested by DSMB member, Dr. Marie Griffin of Vanderbilt, who has published several post licensure vaccine safety evaluations usually similar methods.

The relative risk of all MAARI events including RAD was determined by comparing rates for the zero to 14 days and zero to 42 days after LAIV to those for the

period prior to vaccination and greater than 14 or greater than 42 days after vaccination. Using community virus surveillance as a guide, the data were adjusted for background MAARI rates related to the prevalent viruses such as respiratory sensational virus or parent influenza viruses. Medical records were reviewed by Dr. Gaglani and Dr. Piedra for all day zero events to determine if the illness antedated vaccine administration and all encounters with the 493 asthma code to see if the subject had a wheezing illness at the time that they were seen or they were seen for some other condition. The rates of MAARI before vaccination and greater than 14 or 42 days after vaccination were used as the reference.

The relative risk for all MAARI were less than expected and statistically significant for 1998-1999 and 2001-2002 for preschool children with a history of RAD during the first 14 days after live,

attenuated vaccine. When you look at the smaller subgroups with lower respiratory tract illness or with wheezing illness, we see the same thing that the number of events in the first 14 days was essentially less than expected and this is the period when wheezing occurs with respiratory virus infections.

I forgot to mention in my introduction that we also looked for serious adverse events in this population throughout the period of the study and there were no serious adverse events or hospitalizations related to the vaccine.

Now as I said, we also looked at the period for -- let me make sure I'm at the right place in the slides here. Okay. That's the asthma and the air ID events. Then we also looked at the period 42 days after live, attenuated vaccine and the same general pattern of relative risk was discerned. The MAARI rates one to 42 days post LAIV were

significantly lower for 1998-1999 and 2001-2002. The MAARI rate was slightly higher for LAIV recipients during the one to 42 day period after vaccination in 2001, but the 95 percent confidence interval was broad and spanned one. We saw essentially the same thing for lower respiratory tract illness and for wheezing illness during the 42 days after vaccination.

In conclusion, children one and a half to four years of age with a history of mild intermittent asthma had a decreased risk of MAARI and no evidence of increased risk of wheezing illness 14 to 42 days after -- or 42 days after administration of a live attenuated influenza vaccine by nasal spray.

Children with a history of mild asthma compromise a large proportion, almost 18 percent, of the children in this age group. They should have the advantage of receiving effective protection against influenza. This study demonstrated that a

significant benefit of a single dose of LAIV against both matched and heterovariant influenza viruses with protection extending into the second season.

The decreased risk of MAARI, one to 14 days after LAIV, suggests nonspecific protection against some respiratory viruses. This observation has been reinforced by almost immediate protection demonstrated after LAIV was given to school children during the 2003 epidemic caused by the variant A/Fujian H3N2 virus. From a public health standpoint, LAIV is preferable for children in this age group. Thank you for your attention.

ACTING CHAIR MODLIN: Thanks, Dr. Glezen. I regret we don't have time for questions for Dr. Glezen. Dr. Blaise, Dr. Michael Blaise who is representing the Immune Deficiency Foundation.

DR. BLAISE: Yes. Thank you. I have no financial relationship to Medimmune

or to any of their competitors in this particular area. I'm Medical Director of the Immune Deficiency Foundation and I'd like to change the topic slightly because we are interested in concerns of safety in general with both the agent that's under consideration, agents that you're going to be discussing tomorrow, as well as things in the future.

The Immune Deficiency foundation which was founded in 1980 is the national patient organization dedicated to improving the diagnosis and treatment of patients with primary immune deficiency diseases through research, education and advocacy. In the United States, approximately 250,000 people are diagnosed with a primary immune deficiency disease. Thousands more go undetected. These diseases are chronic illnesses caused by hereditary or genetic defects in the immune system in which part of the body's immune system is missing or does

not function properly.

There are over 130 distinct primary immune deficiency diseases and they affect people differently. For some, the body fails to produce any or enough antibodies to fight infection while for others, cellular defenses against infection fail to work properly. Throughout their lives, people with primary immune deficiency are more susceptible to infections, endure recurrent health problems and often develop serious debilitating disease.

The IBF recognizes the importance and enthusiastically supports the development of new vaccines to help protect the general population and by way of herd immunity, those patients with inherited defects in their immune system. However, we also want to emphasize that the evaluation of potential risks of live agent vaccines to patients with defects in immunity must be part of the development and approval process for these

vaccines.

Over the years, many, many patients with primary immune deficiency have had serious or fatal infections with live agent vaccines including oral polio, BCG, vaccinia, Varicella and measles vaccines. These agents are typically recognized to be a threat to those individuals carrying the diagnosis of primary immune deficiency and appropriate precautions are usually included in the drug insert materials.

However, surveys indicate that the average time from the onset of infections to the diagnosis of these diseases is 9.2 years. Therefore, many individuals have potential risk from live agent vaccines and their physicians and others delivering the vaccines may be unaware of the potential risk that is the problem that addresses to these patients.

The Immune Deficiency Foundation urges that when recommendations for immunization with a new live agent vaccine

are being developed by manufacturers and the agencies that consideration be given to including a warning statement to alert physicians to avoid the use of these agents in patients that may have unrecognized immunodeficiency until appropriate studies have been done to rule out that possibility. These warnings should indicate that the vaccine be withheld for individuals that have experienced recurrent, persistent, severe or unusual infections, particularly if others in the family have had a similar susceptibility to infection.

Further, the IDF believes that investigation of the susceptibility of immunodeficient subjects to SAE from live vaccines and exploration of strategies for treating disease caused by live agents should be considered as an integral part of the drug development and approval process for these materials. Several live agent vaccines are known to have some capability for horizontal

spread to unimmunized contacts, a property that may be useful to ensure greater efficacy in developing herd immunity, but a property that provides yet another risk to potentially susceptible individuals with PID.

As more and more live agent vaccines are entering the marketplace and that some are being adopted for immunization programs to be administered in the schools, the risk of that susceptible individual may receive such a live vaccine agent increases. Very frequently, parents of immunodeficient children ask us for advice about what they should do if a healthy sibling or a playmate must be immunized with a live agent vaccine. Do we keep our child out of school? Do we send the normal sibling to live with grandparents for three months or three weeks until after they've had enough time to experience their vaccine and develop immunity? It's a very significant problem for our patient populations particularly

because the package inserts say don't give this to an immunodeficient patient. How do we come to grips with dealing with what is the actual threat?

Severe-combined immune deficiency or SCID is generally the most serious of the primary immune deficiency and infants born with this disease usually die within the first year of life. SCID infants appear normal until they become infected, accounting for the fact that the mean age of diagnosis of SCID in the United States in the largest series in the United States was 6.5 months of age. Since newborn screening for this condition is currently not being carried out, these infants will continue to receive live agent vaccines scheduled as part of routine immunization practice.

SCID represents a true pediatric emergency since the cure rate using bone marrow transplantation is as high as 96 percent if the procedure is carried out by

three months of age, before the infant acquires a serious infection. The success of marrow transplantation falls dramatically in already infected infants and wild-type influenza virus, both types A and B, have been associated with such problems in children with severe-combined immune deficiency.

In countries where BCG immunization is routinely practiced, infants with SCID regularly develop fatal BCGL from the vaccine that is often administered before the diagnosis has been established. Similarly, paralytic polio has been developed in patients with both agammaglobulinemia and SCID following administration of oral attenuated polio vaccine. As I mentioned, chicken pox immunization has resulted in fatal infection in SCID babies and vaccinia immunization has been a major problem in the past in patients with SCID and T-cell deficiency, such as Wiscott-Elder Syndrome.

A new vaccine which has been recently licensed, the rotovirus vaccine, is an agent that we don't know about the effect of the vaccine in SCIDs, but it's certainly true that children with severe-combined immune deficiency developing wild-type rotovirus infection fall into that group of a greatly decreased success rate following bone marrow transplantation. Again, in vaccines that are given as the rotovirus has suggested at two months of age, most of these patients will not have been diagnosed by the time that immunization is carried out.

Concerning FluMist specifically, although no direct data on the risk posed by FluMist to severe immunodeficient patients is available, in general, IDF believes that on balance this agent, if used widely, will enhance protection of immunocompromised through better herd immunity. The temperature sensitivity probably provides a margin of safety to the inadvertently

immunized or exposed immunocompromised patient.

Following the inadvertent direct FluMist administration of a severely immunocompromised individual, we are somewhat reassured by the knowledge that the agent is Tamiflu-sensitive and recommend initiating such therapy as soon as knowledge of the situation becomes confirmed. However, we believe very strongly that continued surveillance of the development of SAE in this unique population of susceptible individuals must be carried out in long-term follow-up following the introduction of FluMist in the younger, potentially more susceptible patient population. Thank you.

ACTING CHAIR MODLIN: Thank you, Dr. Blaise. At this point, we'll proceed to --

DR. MENDELMAN: Can I make a comment please?

ACTING CHAIR MODLIN: Yes.

DR. MENDELMAN: To the public. My name is Paul Mendelman. I'm a physician. I'm certified and recertified in pediatric infectious diseases. I ran the viral vaccine program for Aviron for six years and then as part of Medimmune vaccines for three years. So I have nine years experience.

I think there are two studies that would be helpful to the Committee to understand. One is AV010 which is a study that we conducted. It was submitted in the year 2000 with the original BLA. That study was conducted in 48 children with moderate to severe asthma. So they had to have an FEV-1 of less than 80 percent predicted. In spite of whatever therapies they were getting from their three sites that conducted that trial, they had to have twitchy lungs and have significant low FEV-1s to be in the trial. It was randomized, placebo-controlled, FluMist versus placebo and in that study, zero out of 24 in the placebo had an asthma

exacerbation and two out of 24 in the vaccine had an exacerbation which was easily treated with bronchodilator therapy.

There were no differences in the daily asthma scores. There were no differences in the nighttime wakening scores. There were no differences in the peak expiatory flow rates across the one month of follow-up after being dosed. So it put it directly into the worst case scenario, put it into children with moderate to severe asthma which is not being asked for in this indication but clearly was shown to be relatively safe and easily treated.

The other study that you should know about which was mentioned by the FDA is AV018. So we conducted a trial which was part of this application in children who got MMR and varovax simultaneously with FluMist in the nose or randomized to get placebo in the nose and there was a third arm that got two doses of FluMist. So 1251 babies, it was

conducted over two years. They were all 12 to 15 months of age and in that trial, there were no safety concerns in the 12 to 15 months age group in regard to respiratory illness or wheezing episodes. So that's relevant to the age of population, 12 to 15 months, and the issue about asthma.

So now let me switch to -- for those of you in the room who are as old as I am and have your VBRPAC 1 and 2 merit badges. We conducted a trial in 4,561 healthy adults 18 to 64, study AV009, in the 1997 season. The same year of AV006, year two, when ACD circulated that was a mismatch what was in the vaccine and in that trial in those 18 to 64 year olds showed high effectiveness. In contrast, the CDC conducted a trial in the same season in Michigan and showed no effectiveness in a similarly designed trial for the TIV vaccine.

We were asked and I don't think there's been any vaccine and you can let me

know after the meeting that's been subjected to so many subgroup analyses by age as FluMist over the years. We were asked to do analysis in 50 to 64 year olds and you've already presented today that it was voted by VBRPAC twice to be safe through age 64. We presented in our original license application for FluMist, the robust analysis for those healthy 18 to 64 year olds with the median age of 38 and the vaccine was as or more effective in those over 38 than those less than 38.

So what I would like to do is encourage the FDA to relook at 50 to 64 year old healthy adults which we know it's safe in. Studies have been conducted by Lisa Jackson in over 200 adults over 65 as part of the original BLA application. They had diabetes, heart disease, chronic lung disease. Studies were conducted by the Veterans Administration in 2215 veterans all of which had COPD. So there is no question

about the safety. The effectiveness lies in the over and under the median age of 38.

I would lastly like to point out that we took one of the original H5N1 isolates from the original Hong Kong 1997 epidemic and we put it into a live, attenuated backbone and we went to the University of California, Davis and we vaccinated chickens and mice and we gave them a lethal challenge of H5N1 and we showed that the live attenuated vaccine, H5N1, can protect chickens and mice. As you all know from press releases the efficacy of FluMist is being studied at centers like Johns Hopkins and others currently and in the same vein as the H5N1 Sanofi aventis vaccine, I think it would be a small, baby step to license 50 to 64 year old healthy adults with FluMist so we can gain more data and have it available so it won't be complicated when that next pandemic arises, which it surely will. Thank you for listening.

ACTING CHAIR MODLIN: Thanks, Dr. Mendelman. Is there anyone else who wishes to make a public comment? Seeing none, I understand Dr. Pratt wants to return to the podium to help focus Committee discussion.

DR. PRATT: At this point, I will now present a short discussion of pharmacovigilence activities and risk management issues for consideration before presentation of the questions to the Committee.

A pharmacovigilence plan provides a safety specification that includes identified and potential risks. Based on controlled studies, safety signals identified for FluMist include wheezing within 42 days after vaccination, respiratory related hospitalizations and overall hospitalizations. Notable limitations to acknowledge about the safety specifications are that the main study excluded children with recent asthma or wheezing within 42 days

of enrollment and children with a history of severe asthma.

The pharmacovigilence plan of the Applicant includes plans for passive surveillance activities including accelerated or monthly reporting and an observational cohort study at an HMO setting in 20,000 vaccinees under age five. The study would have 90 percent power to observe a statistically significant increase in relative risk if the true relative risk were greater than 2.5 for events occurring at a rate of one in 1,000. The study will also be able to estimate rate effects or agent errors.

Regarding risk management, the Applicant proposes two risk management tools, one being the age restriction on the label indication and the other a screening for a history of asthma or wheeze using the vaccine information sheet or VIS.

What is the evidence that removing

subjects with a history of wheezing from analyses would have the desired effect? Removing subjects with a history of wheezing would result in weakening the signal for all-cause hospitalizations in children six to 23 months of age, however, the signals for medically-significant wheezing and medically-significant wheezing hospitalizations remain. Regardless of the history of wheezing, no safety signal was detected in children greater than 24 months. Also of note, passive surveillance data from VAERS that I presented earlier suggest that some people with wheezing get FluMist despite the label warnings.

When considering the Applicant's risk management tools of age and wheezing history, some issues are identified on this slide. Age as a risk management tool is familiar to users as the current label, the indication is restricted by age and also based on the reports to VAERS, it suggested

that this has been successful in preventing children under the age of five from getting the vaccine under the current label.

Regarding the screening on the history of asthma or wheeze, at this point we have no prospective data on the effectiveness of the vaccine information sheet as a screening risk management tool. It's also notable that asthma and wheezing have a relatively high prevalence in children and that there's difficulty in defining the history of wheeze and the history of asthma in the youngest age groups. Also asking providers to determine a history of wheezing prior to vaccination is an additional complication for use in routine practice.

At this point, if the Committee is ready, I'll present the questions for final discussion and voting. Again, the first question, do the data demonstrate the efficacy of FluMist for prevention of influenza illness in the following: (a) the

Applicant's proposed population, that is, children age 12 to 59 months without a history of wheeze; and (b) children in the age strata six to 23 months; and (c) children in the age strata 24 to 59 months?

ACTING CHAIR MODLIN: I would suggest that we focus our initial discussion on this question and maybe just to lead off, I think I know the answer to this question. Well, I know I know the answer to this question, but for Dr. Norman Baylor and for others, I noticed we've not been asked to give an opinion regarding superiority of this vaccine to TIV and I don't know if you want to say anything more about that, Norm, before we go on or should we just leave that off the table?

DR. BAYLOR: I'd leave that off the table and just focus on the question.

ACTING CHAIR MODLIN: Fair enough. Let's have an open discussion and then I think we'll probably fairly quickly try to

bring at least this one question to a close. Are there questions or comments from the members of the Committee specifically about efficacy? If not, we -- yes, I'm sorry. Larry.

DR. MOULTON: I just have a question. Several of the FDA reviewers were talking about the exclusion of the children from the CP111 trial for the severe asthma and so forth. How many kids were excluded for those reasons?

DR. CVETKOVICH: Therese Cvetkovich. We don't have those data, but Ed may.

ACTING CHAIR MODLIN: Ed, do you have the answer to that question? How many kids were actually excluded from the trials based on the exclusion criteria?

DR. CONNOR: We didn't specifically collect who was excluded. So some of that information is available at the sites, but it wasn't collected as part of the

routine data collection.

ACTING CHAIR MODLIN: Not even a guess?

DR. CONNOR: I mean, I think if the total population of kids are going to be with any wheezing is about 21 percent of the overall population which is a reasonable estimate of what we know about wheezing estimates in the young population anyway. It's somewhere between 20 and 30 percent of kids that have at least one episode of wheezing before they reach their first year or so. The kids with severe asthma in that population is a very small fraction of those kids who wheeze and the kids who wheezed recently is hard to estimate because some of those kids actually, although they might have wheezed six weeks ago, waited and then got enrolled and the immunocompromised kids are a very, very small population. So that's about as best as I can do.

ACTING CHAIR MODLIN: Thanks.

Other questions or comments? If not, we don't we actually -- Bruce.

DR. GELLIN: Yes, this is a little bit tangential but with the potential of cross-protection against drifted strains or imperfect match, the question I'm getting at is duration of protection and it doesn't really -- it doesn't state that this is for annual immunization. That's the underlying assumption, but I wonder if you have any information about what the likely duration of protection is in case a year goes by and a child does not get vaccinated and there is some drift, again, if they would get some benefit from what they received before.

ACTING CHAIR MODLIN: Go ahead.

DR. CONNOR: I guess in all the studies that we've done, immunogenicity studies and other things, obviously getting annually vaccinated and getting two doses if you're young are better than other alternatives. On the other hand, we all

recognize, first of all, that kids don't often get two doses even though they're recommended to get two doses and they don't often get annual vaccination even though we would like them to get annual vaccination.

The only data that's really pertinent to that is that we do have some data that looks at one of these trials, the 501 trial particularly that was done in several consecutive years, and there was a group of kids who were not vaccinated in the second year, but followed in the second year and in that group of kids, while the efficacy was lower, it was still 50-ish or so in that population of kids. So there at least is, we believe, relatively longer lasting protection.

The other issue we've been interested in trying to find approaches of vaccinating children earlier so that they can achieve their pre-school visits and those sorts of things and as an effort to get

vaccination rates up and in again one of these studies, we looked at several countries in which the epidemic in those countries was very late, was more like eight-plus months after the vaccination time and there were no differences in the efficacy in that later age group compared to the earlier age group. So that's about the sum of what we have.

ACTING CHAIR MODLIN: Okay. If there are no other questions or comments, I think we will proceed to a vote on this issue. It's actually a vote on this question. There are actually three separate questions. So I'm going to ask each of the voting members and -- Bob Daum.

DR. DAUM: I'm sorry, John. You're moving to summarize and I'm interrupting and I apologize. But can I ask for some clarification on part B if we're going to go right to a vote? It seems to me that we're talking today about an application to extent use of this vaccine downward to

some undefined point or clearly defined point of 12 months. And so what is the purpose of asking us about the six to 12 month old age group? Is that just sort of what do we think of the data we've seen or is that --

ACTING CHAIR MODLIN: You mean the six to 23 month.

DR. DAUM: No, I mean six to 12. I understand 12 to 23. In part b they are. I mean in part b our answer will include children who are six to 12 months of age.

ACTING CHAIR MODLIN: I see.

DR. DAUM: And I think it goes to the safety question that will come on the next slide also. So I'm just curious as to how the FDA or the manufacturer or anybody wants us to view the six to 12 month age group as it might color our answer to the six to 23 month age group.

ACTING CHAIR MODLIN: I think they're interested in our advice in that age group, otherwise, they wouldn't have asked,

would be the short answer, Bob. But maybe Norm Baylor or Dr. Pratt, if you would like to respond.

DR. BAYLOR: I'll start. It's where the strata were as when the clinical trial was divided up. That's where the strata falls.

ACTING CHAIR MODLIN: All right. Seth.

DR. HETHERINGTON: I realize that the question about superiority is off the table, but I want to confess a little bit of confusion on this question. The trial that we're discussing is this recent trial which was set up as a noninferiority trial. It has an active control. So in a discussion about efficacy, we're assuming that the control arm is effective for the virus strains in circulation of that year and I'm not sure how much that would impact our discussion or our declaration that this is --

ACTING CHAIR MODLIN: I can just

point out that we've also seen data from placebo control trials of this vaccine as well.

DR. HETHERINGTON: Right. I understand that. But the age groups that are in that question relate to the noninferiority trial, not to the placebo control trials. So are you asking us to discuss efficacy as displayed by the recent trial or are you assuming that we're including in this discussion data from the placebo control trials which have different age groups and different strata in there?

ACTING CHAIR MODLIN: I think that's on the table. If you would like to discuss it when we come around to you or do you have some more specific questions about that?

DR. HETHERINGTON: I'm raising it as a question, because I find it a bit confusing. I'm not sure how the other members of the Committee think about that,

but perhaps as they go around and give their opinions, they might want to include that in the discussion because, clearly by the criteria of the trial, which was a noninferiority trial with the lower limit of the confidence interval as being greater than -30 percent, it did achieve its goal for all the predefined strata. I think that's obvious, but again, I'm confused by the question about efficacy and how that relates to a noninferiority trial with an act of control on it.

ACTING CHAIR MODLIN: Okay. Dr. Cvetkovich, would you like to address that before we start?

DR. CVETKOVICH: I'll try. I don't think I can directly. This is Therese Cvetkovich, FDA, and again, Medimmune can correct me if I'm describing it wrongly. For the primary endpoint for MICP111, a single confidence interval was constructed so that noninferiority to TIV could be evaluated. If

noninferiority criteria with a lower bound of greater than -30 percent was met, then of course you can see whether it's superior or not and I think if you look at the overall results, clearly we would not accept the lower bound of zero for an effective vaccine, but for the relevant analyses they're clearly well above that. Does that get at it?

DR. HETHERINGTON: I think that's very helpful actually. But previously the comment was made that we weren't -- the discussion around superiority was off the table I think is what was said. But if we're going to have a discussion about efficacy, we have to compare it to something and the something happens to be an active control arm.

DR. CVETKOVICH: I think it's interpretable regardless because you keep in mind the study design and I think that the issue of the word of superiority or that sort of thing we'll discuss that in labeling and I

think you can discuss efficacy without trouble.

DR. BAYLOR: And if that -- if you need to go through that as part of your deliberation, that's fine. But specifically to a vote, we're not asking you to vote whether this vaccine is superior to the control.

DR. HETHERINGTON: That I understand. I was trying to get to whether the criteria by which we declare efficacy if we have an active control arm and I think you've answered the question.

Why don't we move on and specifically have each of the voting members vote on each of these three separate questions and I'm going to start with Dr. Stapleton.

DR. STAPLETON: I think the definition of noninferiority with an active control, based on that, I'm comfortable that the vaccine is effective in the 12 to 59

month group. I think the only groups where there's any question of even perhaps superiority, which we're not voting on, are the matched age six to 23 which comes to question b and then the type B strains. So I'm comfortable that comparing this with the TIV and then all three age strata, I'm comfortable that this is efficacious.

ACTING CHAIR MODLIN: So you're voting yes on all three. Okay.

DR. STAPLETON: Yes.

ACTING CHAIR MODLIN: Dr. Aziz.

DR. AZIZ: I would like to echo Dr. Stapleton. I feel like it's yes for all three.

ACTING CHAIR MODLIN: Fine. Dr. Demmler.

DR. DEMMLER: I think the data show clearly that the vaccine is efficacious in all the age groups.

ACTING CHAIR MODLIN: Fine. Dr. Gellin.

DR. GELLIN: Yes, for all three.

ACTING CHAIR MODLIN: Ms. Hoffman.

MS. HOFFMAN: Yes, for all three.

ACTING CHAIR MODLIN: Okay. Dr. Kercsmar.

DR. KERCSMAR: Yes to all three.

ACTING CHAIR MODLIN: Dr. Hetherington.

DR. HETHERINGTON: I remind you I'm a nonvoting member, but I agree with the other people on the Committee.

(Laughter.)

ACTING CHAIR MODLIN: I'll remember that the next time around. Dr. Moulton.

DR. MOULTON: Yes for all three.

ACTING CHAIR MODLIN: Dr. Wharton.

DR. WHARTON: Yes for all three.

ACTING CHAIR MODLIN: Dr. Self.

DR. SELF: Well, I'm not going to be quite so brief. So as near as I can tell, the two placebo control trials that we've

seen presented go down to 12 and 15 months of age and on the basis of that, I think the answer to a is yes.

The only data going down to six months is relative to TIV and there was no data presented about the efficacy of TIV that goes down to six months of age or what those trends are. I think a lot of this discussion is about trends and I'm finding it very hard to get my hands on this, both in terms of efficacy going in one direction and in the safety outcomes going in the other. So I would have to say no to b based on the data that we've seen so far and c is clearly yes.

ACTING CHAIR MODLIN: Okay. Dr. Jackson.

DR. JACKSON: I say yes to all three.

ACTING CHAIR MODLIN: Dr. Farley.

DR. FARLEY: I'll say yes to all three with the assumption that TIV is effective in six to 23 month olds.

ACTING CHAIR MODLIN: Dr. Daum.

DR. DAUM: And Dr. Farley said it exactly the way I would like to say it. So I say yes to all three with her caveat. That's the assumption on the table and that's what people are having trouble with.

ACTING CHAIR MODLIN: All right. Yes, Dr. McInnes.

DR. McINNES: Yes, to all three.

ACTING CHAIR MODLIN: Okay. Dr. LaRussa.

DR. LaRUSSA: Yes, to all three.

ACTING CHAIR MODLIN: And I'll vote yes to all three as well. I'm glad we're able to do this because it's clearly the next question I think that is going to require the real pointed and difficult discussion of it that we need to have. Why don't we put up if we could the next slide with the question so that everyone can see them. But I will read the question, too. Do the safety data demonstrate that the benefits

will exceed the risk of FluMist for use in (a) the Applicant's proposed population, i.e. children age 12 to 59 months without a history of wheeze; (b) children in the age strata six to 23 months regardless of wheezing history; and (c) children in the age strata 24 to 59 months regardless of wheezing history? And before we vote, I'd like to open this up to questions, comments, discussion that we can all benefit from. Dr. Self?

DR. SELF: Yes. So one thing that I'd like to be clear about, back to the Slide 48 with the rate differences, it wasn't obvious to me that those were based on an intent to treat analysis and I think given the intent of that it would be important that it'd be based on ITT. Can I --

ACTING CHAIR MODLIN: Do you want to answer that question? This is the slide 48, the comparison of risks and benefits which we all agree was an important slide. I

assumed that that was based on --

MS. HULTQUIST: It actually was based on --

ACTING CHAIR MODLIN: I'm sorry. You need to use the microphone and identify yourself please.

MS. HULTQUIST: I'm Micki Hultquist, Biostatistician for the CP111 trial. It was actually based on something we call the safety population which is essentially the ITT population for subjects who received at least one dose. It included all of events starting from randomization through the end of the study.

ACTING CHAIR MODLIN: Good. Are there other questions? If not -- yes, Dr. Stapleton.

DR. STAPLETON: I think a lot of the problem people are having is the idea that if you -- when Dr. Connor showed the data taking away the people who don't have a history of wheeze that you lose that excess

hospitalization and I guess that's really the crux of the matter to me and it's unclear how well screening of large populations will be and the ability to exclude people who are at increased risk and I don't know if Medimmune or others would like to comment to further make me comfortable that that is something that will work in that six to 23 month age group.

ACTING CHAIR MODLIN: Let me understand what your question is. You're concerned about the ability to exclude kids who are at risk by virtue of, at least, the known prior history of wheezing.

DR. STAPLETON: Correct, because it appears that the medical history and the parent history are not always in sync and then large community clinics, the setting where this will be used, I'm not totally comfortable that the setting will be as good as in a clinical trial and I'd like some reassurance, I guess, maybe.

ACTING CHAIR MODLIN: In a real world setting. Ed.

DR. CONNOR: Sure. I've gone through with you what I think basically are the expectations related to how those questions were achieved and the goal in the real world would ideally be to try to mimic what we saw in CP111 so that we could achieve that reduction of the risk in that population.

I think, from our perspective, I guess I could just reiterate that I think that the questions that were asked were relatively straightforward in a relatively small and easy adaptable to the kinds of settings that we're talking about. But on the other hand, we all recognize that sometimes it's not going to be there. Either the parent will be mistaken or the record won't be available or, potentially, someone gets vaccinated inappropriately outside of the label of the product.

So what we have done is done some simulations to look at the effect on a population basis of various levels of error in those choices and maybe I could just ask that Dereck from PAI go through that with us. I think if we -- Can we switch the slide to --

ACTING CHAIR MODLIN: Sure. Yes.

DR. WEYCKER: Chris, is it possible to put up the slide that focused on overall population? I think that would be a good starting point.

Do you have the one that focuses on all kids with and without a history of wheeze? That was part of the backup slides. I think someone had pointed earlier that the slide that corresponds to Number 48 but focuses on all kids with and without a history of wheeze is the one that's most relevant or should be the focus of interest. But I think there is a caveat we need to associate with that particular comment and

that is that the representation of kids in CP111 in terms of their -- or based on the history of wheezer or asthma, it's not necessarily what you'll see in the vaccinated population in the real world. So one would expect that in the real world, the representation of kids who are vaccinated and have a history of wheeze or asthma would not be to the extent that was among the kids enrolled in CP111. So as a benchmark, this is the slide that Ed had presented earlier and again it was noted as the one that should be of focus for the risk/benefit assessment.

Chris, if we can move to the other slide. What we did is we undertook an analysis the projects the impact on selected outcomes of varying the population of vaccinated kids, children, based on their history of wheeze or asthma. The results in this particular slide describe the difference in outcomes per 1,000 kids who are vaccinated age 12 to 23 months and those kids were

vaccinated with FluMist and then alternatively with TIV within the context of this analytic model.

The outcomes you can see in the first column that were considered, CDC-ILI, MSW, medically-significant wheezing and hospitalization. The columns describe the extent to which the population of kids, that is the 1,000 kids in this particular analysis, is comprised of kids who have a history of wheeze or asthma and are within the same age group, that is, they're age 12 to 23 months. Focusing on the first column, that is, with the header of zero percent, that assumes that within this particular population of kids age 12 to 23 months that no kids have a history of wheeze or asthma and we can see the results in that first column. There would be with FluMist among these 1,000 kids who are assumed to receive FluMist a reduction of 35 cases of CDC-ILI per 1,000, an increase on average, and these

are all averages, of MSW of four cases per 1,000 and a decrease in hospitalizations of eight per 1,000.

As we move to the right, and that is, go to columns 2, 3, and 4, the distribution of kids within this population of vaccinees changes and the mix of kids or the representation of kids who have a history of wheeze or asthma increases as we move to the right and thus the representation of kids who don't have a history of wheeze or asthma decreases. So the pie in terms of the absolute size stays the same. So as we move to the right, we have in the second column three percent representation of kids among the vaccinees who have a history of wheeze or asthma and then six percent and the 19 column corresponds to the results from CP111. That is, if all kids in the real world who were vaccinated with FluMist, if that distribution, the distribution of those kids by their wheezing status was comparable to

what was observed among the enrolled kids in CP111, then those would be the expected results.

However, I think it's important to note that we're probably not going to end up in a situation where the distribution of kids in the real world who are vaccinated is consistent with what was observed in CP111. Obviously the extent to which that occurs is based on the effectiveness of the screening strategy. So to the extent that the screening strategy decreases the vaccination rate among kids who do have a history of wheeze or asthma, then we're going to end up to the left of that fourth column, the three percent and the six percent are what we feel are reasonable expectations about the representation of kids with a history of wheeze or asthma in this particular age group and that's based on findings from CP111 that are noted in the footnote.

I think that the main take-away

message from this particular slide as the outcomes is as you move to the right, that is move from the first column to the second and third, that the outcomes remain relatively constant, that the change in those, in absolute terms, is relatively small.

ACTING CHAIR MODLIN: Thank you. Dr. Hetherington.

DR. HETHERINGTON: Just a question on this. This was all relative to TIV. Is that right?

DR. WEYCKER: That's correct.

DR. HETHERINGTON: And that brings me back to my original comment. I think the concern I had in assessing the efficacy question gets compounded when trying to assess risk/benefit. For instance, in the FDA briefing document in the appendix, there's a table which calculates a risk/benefit based on expected outcomes for the different age groups and tries to assess the risk for additional episodes of

medically-significant wheezing with the benefit for reducing frequency of infections or numbers of infections. The problem is that that's relative to TIV.

So if the question that we're being faced with now is to assess risk/benefit, the study that we're looking at something that compares it to TIV. If we're trying to assess risk/benefit for this particular vaccine on its own, then I think these kinds of numbers over estimate the risks and under estimate the overall benefit. In other words, if you're trying to figure out if you give kids age 12 to 23 months vaccine, how many new cases of wheezing do you create versus how many cases do you prevent had you given them nothing? That's a totally different analysis than what we're looking at with these numbers. But I think that's the analysis that you're asking us to make in order to assess risk/benefit.

ACTING CHAIR MODLIN: That's a

good point but we just need to point out that influenza vaccine is recommended for all children between six and 23 months of age, actually six and five or six years of age now.

DR. HETHERINGTON: I understand that. What I'm saying -- but that's not one of the questions that we're being asked.

ACTING CHAIR MODLIN: Dr. Jackson.

DR. JACKSON: Just in thinking about this whole risk/benefit question, I have a couple considerations that may or may not be useful for the Committee. It's sort of along the lines of what you were saying, Seth. I mean the other issue is that we're looking at numbers and we're comparing three versus eleven versus four. But I think we're in error for weighting those the same way because the magnitude of the risk of burden of illness from a medically-significant wheezing event that's self-limited and relatively mild is not equal probably to the

burden of illness from getting influenza and so I don't think we should necessarily just be subtracting one from the other, although I don't have any other -- other than just sort of a general qualitative sense to do that without additional information.

I mean the other thing is that at least I found a helpful perspective that if we have a live virus vaccine, we're going to expect to see some adverse events following immunization that are related to viral replication or the immune response to viral replication. So just putting it in context, I think it would be helpful to consider FluMist in terms of the safety profile of other licensed live viral vaccines like rotovirus vaccine or Varicella where we do expect to see some viral replication complications, if you may, and that's probably what this wheezing is.

Secondly, with regard to what question we're looking at FluMist versus

nothing or FluMist versus TIV, I understand that the context of the risk/benefit analysis have been sort of an assumption that we have a population and they're getting either FluMist or TIV. In the real world, it's possible that there may some children who would only get TIV or perhaps a larger group of children who would get LAIV when they would not get TIV. So it's possible, although impossible to quantify. There could be some additional value from children who are getting the full benefit from LAIV versus nothing, as Seth said.

And lastly, I think as Jack brought up, I mean, for general context, imposing a restriction on children with a remote history of wheeze seems perhaps not biologically relevant and I believe would greatly complicate vaccine delivery and so I think that's another qualitative consideration that we should keep in mind.

DR. BAYLOR: Dr. Modlin.

ACTING CHAIR MODLIN: Yes. Dr. Baylor.

DR. BAYLOR: Yes. Melisse Baylor from the FDA. I just wanted to add something to your question, Dr. Stapleton, about the usefulness, basically, of this history of wheezing as a screening tool. First, the history of any wheezing as a screening tool was post hoc. They had originally used protocol diagnosis which was three episodes or more. They saw that that wasn't very useful. So they went back to any history of wheezing at all by the parent or guardian or the medical record and that does reflect more of what you're going to see in the real world.

But there is a problem with this in that if you try to vaccinate a one year old, you're not going to have -- there are not that many one year olds that have wheezing except the ones that probably went through the winter and got some

bronchiolitis. So those are problems and I just wanted to reshow you this slide and to let you know these are all subjects with a history of wheezing at study entry and as you'll see, it's done by age. So if they had a positive history, how many of those 322 with a positive history had a wheezing event after vaccination with FluMist? And this is only the FluMist arm. So TIV isn't even taken -- I take that back. That is TIV. Sorry about that.

But if you look at only FluMist, you see that 77 of 323 or 23 percent did wheeze after they got FluMist. Now that's higher than the 24 to 35 month old I think largely because if you're little and you wheeze you probably have a little bit worse case of chronic wheezing. But I think the most important thing to me about this slide is to look at 23 percent as a predictive value is very low. So my opinion asking for a history of wheezing is (1) it hasn't been a

tool that's been tested officially and (2) the information we do have didn't seem very useful.

ACTING CHAIR MODLIN: Bob.

DR. DAUM: So --

ACTING CHAIR MODLIN: Bob, I think Ed would like to address specifically that issue.

DR. CONNOR: Yes, I just want to make sure that when we are talking about the risks and the benefits, that we are actually keeping the apples and apples comparison, at least the apples and apples that we have thought about. Maybe there are different ones that you guys need to think about.

We believe that a history of wheezing is a valuable differentiator for the all-cause hospitalization outcome. We don't understand the all-cause hospitalization outcome particularly. But it is in that outcome that we've seen some differentiation.

When you look at a history of

wheezing, as a predictor of what was happening in relation to the FluMist differentiation, we actually don't see that as a prime differentiator.

That is, you know, a history of wheezing predicts your likelihood of wheezing again but did not seem to be as good a predictor of the differential between CAIV-T or FluMist and TIV as it is for just whether you are going to wheeze again.

So, you know, our getting to the history of wheezing thing really came, I think as somebody pointed out, through the hospitalizations item. We agree that when you look at history of wheezing as a predictor of the difference between the two groups going forward for medically significant wheezing, it is much less. It is much less.

DR. M. BAYLOR: Can I --

ACTING CHAIR MODLIN: Thanks, Ed. Bob?

DR. M. BAYLOR: Oh, can you --

ACTING CHAIR MODLIN: I'm sorry. Dr. Baylor?

DR. M. BAYLOR: Can you back so I can ask you a question?

DR. CONNOR: Sure.

DR. M. BAYLOR: You know I know that in the past you have said in the six to 11 month old, regardless of history of wheezing, they had an increase of all-cause and respiratory and most of them are after 42 days and there is no biologic plausibility.

Now, then you look at the 12 to 23 month group and there is an increase in the wheezing, also late, but only in the patients with a history of wheezing.

But can you explain the all-cause? Why would -- what is the reason that a history of wheezing would have an increase in all-cause hospitalization? Because you know the majority were things like gastroenteritis, which wheezing shouldn't

predispose you to. So --

DR. CONNOR: Yes, I absolutely agree. And I think that we are puzzled by the observation. But the observation is consistent through all the groups that we've looked at. And I can't explain -- I mean because I don't think there is an increase specifically in a differential distribution of those causes either.

There's basically a distribution of -- an increase in each of the groups regardless of whether it is GI or whether it is respiratory or whether it is others. And yet in that six to 11 month old category, whenever we look at it, we find an increase that changes a little bit when you use history of wheezing. And then above that, the history differentiates them.

So I don't know. We were -- that's why we believe that we need to do more there because the observation in a randomized trial was that that was what we observed.

DR. M. BAYLOR: You know I guess that, you know, my point is history of wheezing, as a risk factor tool to minimize hospitalization, it is hard since it seems like almost a statistical blip. It is very difficult to understand why it would actually work as a screening tool.

ACTING CHAIR MODLIN: Dr. Daum?

MEMBER DAUM: Thanks, John.

I have three points to make and I will try to make them succinctly -- as succinctly as I can. The first one is I don't like question two.

(Laughter.)

MEMBER DAUM: And the reason I don't like it is because I'm not used to sitting in this capacity and thinking about risk/benefit. I would prefer to focus on risk and focus on benefit. And then leave it to a different forum, in a way, to do the risk/benefit analysis.

First, I guess, on the positive

side I'd say that it is delightful to think that people are starting to talk like this about vaccines again because we had a long sort of dark period when risk was just unacceptable. And people almost lost sight of the benefits of vaccines.

And so risk/benefit analysis, in a way -- and I know it sounds like I am contradicting myself but I'm really not -- is a refreshing thing to think about.

But there are two ways to think about it. One is -- at least two ways -- scientifically, we can sit here and reflect on what we think is the risk of a little increase in hospitalization, no deaths, versus the benefits of influenza protections. That's a nice discussion that clinical scientists can have.

But the public's perception of risk/benefit may be very, very different than ours. And I'm not sure we are completely out of the woods in terms of thinking that the

public is going to tolerate the kind of risk that we might say is okay to counterweight benefit.

So I guess I'm very uncomfortable trying to do that kind of analysis with this question. And would prefer to focus on whether we think the risk level in these age groups, with and without wheezing, is acceptable. So that's my first point.

And a lot of heads have nodded around the table as I have said it. And so that I think that there is sympathy, at least, for concern about this.

The second point is a fairly straightforward one. And I'm sure someone could clarify it. But when we are talking about wheezy diseases -- and I like Paul Mendelman's comment -- I loved it, in fact, twitchy lungs, and pneumonia, I think we had better hear a little more about the pneumonia cases because this could be a little bit of transient atelectasis or could be the severe

necrotizing pneumonia we've started to see with epidemic staphylococcal disease or anything in between.

And so I'm not sure I know what to conclude from hearing about rates of pneumonia. And I'd like to hear a little more about that.

And then the third -- the last point I would like to make is that the history of wheezing is a tool that -- I think someone said it earlier -- it hasn't been studied to the point where we can really make definitive conclusions about what it means to leave it in or leave it out.

But I'd like to focus for a second on Dr. Ahnn's presentation where he reminded us that in this important trial that we were talking about this morning, people with a history of wheezing were excluded from the study. And that having been said, there was substantial, in my view, medically significant wheezing that occurred in

children six to 11 months old, not different from children 12 to 23 months old.

And so I guess I'm -- did I say something bad?

PARTICIPANT: No.

MEMBER DAUM: So I guess that I'm -- just to finish so Dr. Connor can tell me I'm wrong about each of these points, I'm concerned about not understanding the importance of history of wheeze although on balance it makes sense to think that if they have such a history, we probably wouldn't use this vaccine right now.

But moreover, I'm more concerned that the history is going to turn out, based on the fragmentary data we saw, to not be helpful because plenty of kids who had a negative history still had problems. And the problems didn't seem to go away in young infants, younger than two years of age.

So I'm done. But those are three separate points. And I hope we will talk

about all three of them.

ACTING CHAIR MODLIN: Good. Bob, I assume most of your comments are focused on the 23 months and younger age group. Is that fair>

MEMBER DAUM: All.

ACTING CHAIR MODLIN: Okay.

MEMBER DAUM: All, but I don't want the risk/benefit comment to go by the boards because in a way that is the most concerning part of what I had to say.

ACTING CHAIR MODLIN: Dr. Connor, did you want to respond?

DR. CONNOR: I just wanted to clarify -- Bob, just to clarify the fact that there was not an exclusion for a history of wheezing. The only children that were excluded were children with severe asthma or children who within the past six weeks had actively wheezed.

But you could get into the trial if you had a history of wheezing. As a

matter of fact, we wanted to include as broad a group of kids as possible and only exclude those kids that we specifically didn't have any data for.

MEMBER DAUM: So what would you like us to conclude about then with people without a history of wheezing just in terms of the Part A of this question?

ACTING CHAIR MODLIN: Bob, maybe you could explain? I'm sorry. From your last question, you know, maybe you could elaborate.

MEMBER DAUM: I'm looking at Part A. And wondering what we are to think about this risk/benefit in children in this age group of kids without a history of wheeze. I mean if, in fact, they weren't excluded or were excluded, how can we infer what the risk/benefit ratio is vis-_-vis that history?

Is that more clear? Or still muddy?

ACTING CHAIR MODLIN: Not to me

but --

MEMBER DAUM: So I'll try one more time and then I'll stop. Children 12 to 59 months of age without a history of wheeze, those children were, in fact, entered into the trial. And so have we seen sufficiently stratified information about those who gave that history and didn't give that history relative to events occurring after immunization? That's as clear as I can say it. If it's not good, I apologize and I'll stop.

ACTING CHAIR MODLIN: My sense is that that was Slide 48 that was originally presented. While we are getting that -- we'll come back to that.

Ms. Hoffman, yes?

MEMBER HOFFMAN: Yes, I just want to, I guess, support Robert's position in terms of quantifying risk/benefit from a patient perspective or a parent perspective. It is very difficult to do.

I mean if you, you know, take an example, okay, I have eight children, three preschoolers under the age of five. Can I manage economically or physically having one of those children hospitalized for X number of days because of increased, you know, medically significant wheezing.

Or have to deal on a daily basis with wheezing episodes as the result of influenza versus, you know, having, you know, my kids have the flu and are still at home and manageable and whatever. You know I think that's very much a qualitative issue per family.

And, you know, whereas one family maybe they could afford the hospitalization, you are dealing with young families, who, you know, they might not have, you know, even medical coverage. So that I think there are a lot of factors and, you know, risk/benefit, you know, this question is very, very hard to quantify for families on an individual basis.

So I, too, would, you know -- it is much easier for me to answer that question in terms of risk as opposed to risk/benefit.

ACTING CHAIR MODLIN: Good point.

Dr. Baylor?

DR. N. BAYLOR: I'd like to try to clarify that question a bit. I mean in essence, we've always asked that question. But it hasn't been this directly. When you evaluate, when you ask, when you answer the question about the safety of vaccine in relationship to the effectiveness of vaccine, you are taking that into consideration.

That I'm looking at the safety profile but I'm looking at that not in the absence of the effectiveness of that. And so you are weighing risk/benefit. And we are asking here with the signals that we've seen, you have to take that into consideration in each of the categories that we are asking here.

So I mean that is the kind of

information we are trying to get from you. If I ask you the question simply are the safety data sufficient to support the use of this vaccine, you still have to, in your mind, take into consideration the effectiveness of the product, am I going to be, in simple terms, in a plus category? Am I going to cause more harm from using this product or not?

And so you really have to weigh that vaccine. If it is very effective, then, you know, that is going to influence the safety profile. But you don't -- where is the balance?

And that is what we are trying to get from you with each of these age groups. I mean what is your recommendation? What are your opinions on the safety of this vaccine in light of what has been presented today? But taking into consideration the benefit of this vaccine as well.

And I don't know if that clarified

anything, Bob.

MEMBER DAUM: Norm, of course it does. And if you had a vaccine that prevented HIV but caused you to have surgery to remove a small part of your upper forearm, we would say that that is probably worth it because you are preventing a fatal disease.

On the other hand, that is a pretty significant safety problem. So I would like to have my opinion asked about both of those things. And come to a conclusion separately to advise you.

So I think we have to consider the risks of the use of this vaccine in these age groups independently. And then we also -- you are perfectly right -- have to consider it versus the disease that we are trying to prevent. And give you that risk/benefit analysis as well.

And that's fine. But the question just goes to the risk/benefit analysis.

ACTING CHAIR MODLIN: All right.

Dr. Kercsmar?

MEMBER KERCSMAR: I have a question or a concern that may not be addressable at this point but particularly in this younger age set -- Part B, there is whether what we are seeing in the increased risk for all-cause hospitalization, bronchiolitis, wheezing, any respiratory or other symptom is, indeed, probably an infectious or an immune response.

But maybe particularly in that very young age set is this something that is not just transient but this agent could be a more significant immunomodulatory factor in the upper airway. And then hence the lower airway in these children. There is certainly great interest now in the hygiene hypothesis and the gene by environment or infectious agent by environment causes of asthma and prolonged wheezing.

And whether it is a good influence or a bad influence probably really depends on

the timing of the infectious agent in the respiratory tract and other environmental exposures.

And I don't know if any thought has been given to whether or not a live attenuated viral vaccine in the nose of a very young infant early on is either going to turn out to be a good guy or a bad guy.

And is the immune modulation that goes on something that is going to be temporary, reflected by a transient wheezing episode or is it somehow changing the barrier function of the airway that may predispose to other processes down the line.

And it may be another reason to think about why introducing an agent that we are not sure what is going on in the very youngest subset without further long-term data, maybe it is going to get to what should be further post-marketing monitoring. And something that should come into consideration as a potential risk.

ACTING CHAIR MODLIN: I was going to say I think that is a very interesting question. And obviously one that we don't have the data here to even begin to address. But it might be something certainly for the sponsor to think about longer term.

But I think that we will be getting at those issues when we start to talk about Question 3.

Dr. Wharton?

MEMBER WHARTON: Yes, I just want to echo the previous comment. This has been the thing that has been gnawing at me through really my entire review of this material. The wheezing that has been seen in the studies does not appear to be life threatening. It is there but we don't understand it.

And it seems to a risk that goes on over a long period of time. It is not confined to the immediate post-vaccination period as I understand it. And so is this an

indicator of something that is the result of administering this live attenuated vaccine to very young children of an age that we do not expect uniform exposure to influence a virus to occur naturally?

So maybe this is something that, in fact, we really haven't seen before. And I don't have a strong basis to say that I strongly feel this is the case. But I'm not sure that it is not. And it concerns me a lot in thinking about how to interpret the safety data for this vaccine, particularly for the youngest children.

ACTING CHAIR MODLIN: Good points.

Are there any other questions or comments before we vote on the issue? I just had one further one.

Keep in mind that the pivotal trial here was conducted over a period of one year. And we heard from Dr. Belshe that it was, if anything, a usual influence, a year, maybe a lighter year than we otherwise expect

on average.

And whether or not the risk/benefit ratio would change, as it probably would under circumstances when we had influenza strains that caused more severe disease, particularly when we are talking about a vaccine that has the potential, based on the data that have been presented, to do a better job of protecting against non-well-matched strains in the vaccine.

So that in those circumstances, the risk/benefit ratio is likely to change from year to year. And we are only really focusing, unfortunately, on a very, very small epidemiologic time period here.

And so I think this is something else that the Committee is going to need to keep in mind as we are weighing risk and benefits of this vaccine.

Are there other comments? If not, I think we are going to start with Dr. LaRussa in the hot seat.

And, Phil, I'm going to ask if you would address each of these three questions and let us know how you feel about them.

MEMBER LaRUSSA: Sure. Thank you for the opportunity to answer first. And I'm going to muddle through these in reverse order.

I think I'll say yes to C. I'm pretty happy with the data for 24 to 59 months.

As far as B goes, I'm a little uncomfortable. And I'm uncomfortable with the post hoc staff division of the six to 23 months and into six to 11 and 12 to 23 months.

And I'm also not convinced that the benefit outweighs the risk in the 12 to 23 months without a history of wheezing. And that, I think, is because of there clearly is a benefit in terms of preventing influenza.

But I'm bothered by the increase in wheezing. And also the fact that the

benefit for hospitalizations is relatively small.

And finally because I think there is an acceptable alternative in that age group. I'm going to say no to B.

And because of no to B, I guess I have to say no to A also.

ACTING CHAIR MODLIN: Dr. McIinnis?

MEMBER McINNES: I'm persuaded that the data do support a small and consistent increase in hospitalizations and wheezing and respiratory events in children 12 to 23 months. I think the history of wheeze as a screening tool is not robust. And it doesn't help me embrace the respiratory signal in this 12 to 23 month group.

So it seems to me that the rationale that was put forward to exclude the six to 11 month group really extends to the 12 to 23 month group. So I vote no on A, no

on B, and yes on C.

ACTING CHAIR MODLIN: Dr. Daum?

MEMBER DAUM: Nothing to say that hasn't been said. I am no, no, and yes.

ACTING CHAIR MODLIN: Yes, he is no, no, and yes.

Dr. Farley?

MEMBER FARLEY: The same. Yes, no to A, no to B, and yes to C. And a robust yes to C. I mean I want to emphasize, you know, that this is apparently a quite good advance to have this available for 24 to 59 month olds. But I have the same cautions that others share about the subgroup analysis.

ACTING CHAIR MODLIN: All right.

Dr. Jackson?

MEMBER JACKSON: I'll start with the last first. For C, I would say yes. And I see no reason to restrict the 24 to 59 group by history of wheezing or other factors. There appears to be no safety

signal there. And that would only complicate matters.

For B, I would also say yes. Unlike some of the other members of the panel, I guess I'm not as convinced about the efficacy of TIV. And so one of my considerations is that if we are to administer vaccinations to children, they should be ones that are efficacious in preventing infection. And the data are pretty scant for TIV. So I think we have shown that this vaccine does prevent more influenza illness than TIV. And perhaps that is greater than something that is close to zero.

The safety signals are by and large limited events that were carefully assessed and probably many would not come to medical attention in the absence of a clinical trial.

So I think further follow up would be needed post-licensure for certain. But

that I would say yes to B. And, of course, also yes to A.

ACTING CHAIR MODLIN: Dr. Self?

MEMBER SELF: So for A, yes, based on efficacy data that we have seen in the placebo controlled trials down to age 12. And also based on the fact that the -- in the famous Slight 48, that relative benefit is relative to TIV. And, therefore, I think really understates what the benefits of this vaccine is.

For B, no, based on lack of any data that I have seen today on efficacy down to six months of age. And a pretty steep increase in the risks for month six to month 12.

And for C, yes.

ACTING CHAIR MODLIN: Fine.

Dr. Wharton?

MEMBER WHARTON: I do remain concerned about the safety profile in the six to 23 month age range. And for that reason,

I would vote no on both A and B.

On C, I would vote yes but I'm a little concerned about the regardless of wheezing history given that children with asthma and in relatively severe wheezing history were excluded from the large safety study. So I'm not quite sure what regardless of wheezing history means there.

But I'm not sure we can ascertain wheezing history all that well anyway. So I guess I would say yes.

ACTING CHAIR MODLIN: Okay. Thank you.

Dr. Moulton?

MEMBER MOULTON: For A, I would say yes. However, that is just answering the question about the relative benefits compared to the risks. Whether it should be licensed down to 12 months or not based on this, you know, determination of history of wheeze is another question which I'm not answering on that part. I'm just answering would the

benefits outweigh the risks? And I would say yes.

For B, I am saying no. However, if the B were phrased 12 to 23 months, I would say yes. And that is based on the FDA's Table 15 in their briefing document which shows for 12 to 24 months, 42 hospitalizations for FluMist and 45 hospitalizations for TIV.

And for me, you know, I guess what Ms. Hoffman was saying was that this is what really let's you compare things. I have a hard time not being a medically qualified person comparing wheezing to flu episodes and so forth. But hospitalizations puts it all in the same footing for me. It's too bad we didn't have any data on loss of days of work of parents and that kind of stuff. But hospitalizations really -- you know, when we look at that for that age group, 12 to 24 months, there is nothing to choose from between these two because that is a mix of

both risks and benefits in there. So I'm saying no to B because the six to 12 makes me nervous. I'd say yes if it were 12 to 23.

And for C, I'm saying yes.

ACTING CHAIR MODLIN: Yes?

MEMBER FARLEY: No, no, and yes.

ACTING CHAIR MODLIN: Dr. Hetherington, you don't have a vote but you have an opinion.

MEMBER HETHERINGTON: I really don't have any additional comments besides the ones that have been made so far.

ACTING CHAIR MODLIN: Okay, thanks.

Dr. Kercsmar?

MEMBER KERCSMAR: I will vote yes for A because I do think the benefits of the vaccine probably outweigh the risks.

No, for B, because of my concerns about the effects in the youngest strata, the six to 12 month.

And yes to C largely for the

reasons that have been already verbalized.

ACTING CHAIR MODLIN: Thank you.

Ms. Hoffman?

MEMBER HOFFMAN: No to A, no to B, and yes to C.

ACTING CHAIR MODLIN: Thank you.

Dr. Gellin?

MEMBER GELLIN: Well, I came here with the same question that Bob asked. And was confused about the way the questions were framed.

And further confused -- and, again, we are advising -- our role here is to be advisory to FDA on a licensure decision or a decision about new indications when the manufacturer is seeking indications for 12 to 59 months and the questions don't actually align with that.

So we will answer the question because that is what we were asked to do. The questions were great for generating a discussion. How that translates into what

the Agency does with this is going to be complicated. So that is the preamble.

But, again, I found that a little bit complicated given that the ages, specifically that the sponsor was seeking, didn't really align with the questions. That said, I also found it easier to start from the bottom up.

So C, yes. B, no, for the reasons that were already stated. I don't have anything else to add. And A, yes.

ACTING CHAIR MODLIN: Thanks.

Dr. Baylor?

DR. N. BAYLOR: I hate to interrupt the flow but the indication that was put up from the sponsor that was 12 to 59 months, it is in A. You made the comment in fact.

MEMBER GELLIN: That's right. But the questions don't actually give you anything to talk about specifically on that. They give you a broader range based on the

strata of the trial. But we can talk about it.

ACTING CHAIR MODLIN: Dr. Demmler?

MEMBER DEMMLER: I recognize that the safety signals are real and they are measurable and they are different between the groups. In my opinion, they are not clinically significant enough to deny this vaccine to the younger age group.

And so I would actually propose you rephrase and eliminate the words without history of wheeze from A, B, and C. And it would make it really simple then. And it would be to consider its use in ages six to 59 months.

But if I have to answer each question, then I would say yes to all of them. But I really would like the word wheeze taken out.

ACTING CHAIR MODLIN: So a qualified yes to all three. And the qualification is you are not happy with the

inclusion of -- exclusion of patients -- of children with a history of wheezing.

MEMBER DEMMLER: Yes, I think that complicates things and really doesn't -- I don't think it will decrease any measurable adverse events.

ACTING CHAIR MODLIN: Dr. Aziz?

MEMBER AZIZ: My vote is yes for Question A, no for Question B based on the hospitalization and the wheezing data, and yes for C.

ACTING CHAIR MODLIN: Thank you.

Dr. Stapleton?

MEMBER STAPLETON: I vote yes for Question A, and B, a qualified yes -- I'm sorry, a qualified no. I think no for sure for the six to 11 age group, which is not under consideration for licensure.

But given the efficacy data and the question, as stated, for cost benefit, I think the 12 to 23 month is a yes. But the way the question is answered, it is a no.

ACTING CHAIR MODLIN: Okay.

MEMBER STAPLETON: And C, yes.

ACTING CHAIR MODLIN: So yes, no, and yes. A qualified --

MEMBER STAPLETON: No.

ACTING CHAIR MODLIN: Okay.

I'm going to vote yes on all three questions. I do so on the basis of the fact that the morbidity of influenza, particularly in the youngest age group, is extremely high. Obviously it drops off after one to two years.

And when you compare that to the potential benefit, granted we don't have all the information that we would like to have, it seems to me that given the amount of information that we do have, this is the best estimate of benefit at this time.

Also, the differences in wheezing and the differences in hospitalization between the two groups, even though they were either numerically statistically significant,

the actual differences were small.

I think that, compared to the likely morbidity and prevention of hospitalization in this age group, makes me think that this would be a vaccine that would useful down to 12 months of age.

I haven't been keeping a tally so that I'm going to ask Christine to summarize, if she would.

MS. WALSH: Question No. 2A, there were six yeses -- I'm sorry -- Question No. 2A, there were nine yeses, six nos, zero abstain.

Question B, there was three yes, 12 no, zero abstain.

And on Part C, there was 15 yes, zero no, zero abstain.

ACTING CHAIR MODLIN: Okay.

Dr. Baylor, Dr. Norman Baylor, is this the sort of advice that you have been seeking? Is there anything -- I mean this is the time to probe the Committee on the

responses that you have heard in terms of --

DR. N. BAYLOR: No, I think this has been useful. I mean really what we are trying to do is really, you know, hone down and really understand how if this vaccine is approved, how it is labeled and what the indication will be. So I think this has been very useful.

I apologize for the misunderstandings of the question though.

ACTING CHAIR MODLIN: Okay.

Let's go on to the third question if we could which I think may allow us to be a bit more imaginative. And that is -- the third question is if approved for children less than five years of age, what additional postmarketing studies or surveillance activities would you recommend?

I think the best way to address this would be to, again, go around in order. And have each of us weigh in. This is a little bit more of a qualitative than a

quantitative question.

Dr. Stapleton, do you want to start?

MEMBER STAPLETON: No, I'd prefer not to but not being a pediatrician, I honestly do not feel as qualified to discuss surveillance in pediatrics. I'll be happy to vote when we are done. But I don't have much to say.

ACTING CHAIR MODLIN: Okay. I think this is going to be more advice, I suspect, than actual questions that we will need to vote on would be my guess unless something really comes down that is particularly contentious.

MEMBER STAPLETON: I do think that the main questions to address are what happens to wheezing and hospitalization in this age group. And I guess I would defer to my pediatric colleagues for more advice.

ACTING CHAIR MODLIN: We're just not going to pin him down.

Dr. Aziz?

MEMBER AZIZ: I would like to refer to Slide No. 50 by the sponsor. And I think what they are proposing is kind of legit, kind of adequate --

ACTING CHAIR MODLIN: Okay.

MEMBER AZIZ: -- on Slide No. 50.

ACTING CHAIR MODLIN: So maybe for the purposes of discussion, maybe we could put Slide 50 up? In other words, you are comfortable with what the sponsor has proposed?

MEMBER AZIZ: Yes, sir, yes.

ACTING CHAIR MODLIN: Dr. Demmler, you can't hide from not being a pediatrician.

MEMBER DEMMLER: Well, I think it is, of course, very important to continue ongoing observation for incidents of the observed adverse events as outlined.

But what I would also like us to maybe consider is to try and see if we can determine the etiology and maybe the

pathogenesis of these observed wheezing events. I'm still no convinced they are due to the vaccine or vaccine related.

Could they be, you know, co-infections with another virus? Or is there, perhaps, something that is race or ethnicity related or immunogenetic or something else that might predispose these. So perhaps some basic science approach to determining maybe the etiology.

And the other thing is some more effort on Type B and to maybe help us determine why this vaccine and other vaccines are not quite as effective against B. It is probably a bit broader than maybe you wanted but those are some ideas.

ACTING CHAIR MODLIN: Okay.

Dr. Gellin?

Could I go back? I understand in some of the studies, you know, or at least one pivotal study there appeared to be less effectiveness against B strains. But in

other studies, there did appear to be considerable effectiveness.

So I think there has been a mix from study to study. It probably has to do with match between vaccine and all the other factors we have been talking about.

Bruce, I'm sorry.

MEMBER GELLIN: Dr. Demmler talked about an opportunity to look at some upstream basic science. Mine is actually more along the lines of sociology and communication.

Pamela, in her comments, talked about that wheezing as a screening tool really doesn't -- and that was under the key reservations -- and trying to get some better understanding of that to try to figure out what actually to put in a vaccine information statement if that is going to be the vehicle that helps.

And to help practitioners figure out what the best conversation they are going to have with patients who have read the

headlines about this with the reservations. And are not sure exactly how to navigate the discussion.

ACTING CHAIR MODLIN: Good points.

Ms. Hoffman?

MEMBER HOFFMAN: I just want to support the statement that was made by the gentleman from the Immunodeficiency Foundation, sorry. I am actually a parent who had a daughter who had acute myelogenous leukemia and had a bone marrow transplant.

There were four siblings at the time. And they did need to get a live virus because they were young children and get vaccinated for varicella and other immunizations.

And it did create a huge problem in our family in that I had to send those children that were getting the live virus vaccines out of our home for months at a time. So, again, it is a very practical issue.

And at any point in time, there are 30,000 children on cancer therapy in this country. They are surrounded by siblings as well as in the school environment. And if you do get into immunizations within the school and, again, with the live virus, that can pose major problems for immunocompromised children.

And I just think that there needs to be some, you know, studies on that and some labeling and definitely some flags going to the label about that.

ACTING CHAIR MODLIN: Dr. Kercsmar?

MEMBER KERCSMAR: I agree with pretty much everything that has been said. I think it will be important to continue to follow up on who gets hospitalized, try to get some idea of why, maybe find out if you can identify who might be at significant risk here.

And, again, following up on these

kids that do develop wheezing, new asthma, and try to get a handle on whether that is going to be a significant or a transient issue.

ACTING CHAIR MODLIN: Dr. Hetherington?

MEMBER HETHERINGTON: I think what the sponsor has recommended is very good. With such infrequent events being counted, you need a large database. That, by default, I think means it has to be observational or at least database dredging.

The challenge to the sponsor is going to be one, trying to keep it compact enough to be possible as opposed to collecting too much data that would never get analyzed. And, on the other hand, making some assessment as to the completeness of the data that is collected.

In other words, are you capturing all the hospitalizations? Or are the kids going outside of their usual network to be

hospitalized somewhere else?

So some way of assessing the adequacy of the data collection I think will be important as well as keeping it a very succinct and to the point observational database.

ACTING CHAIR MODLIN: Dr. Moulton?

MEMBER MOULTON: Well, I'm a little bit hazy as to what exactly was done for the five to 49 group there. But I would suggest studies in more than 20,000 people in terms of perhaps use of Vaccine Safety Datalink-types of databases, ones that cover, you know, in an observational study, of course, a much larger group of people mainly to look at things such as mortality and how often kids who are immunocompromised are getting it, questions like that. You know in a much larger group of people.

I'm interested, from the academic standpoint, in some of the benefits. I'd like to see studies on indirect effects

within the family, the possible beneficial effects in reduction of flu among elderly caretakers and so forth of these young children.

I'd also like to see more studies on the second year of protection because, you know, it is almost impossible for families to immunize all their kids every year. There are going to be a lot of kids that go second year without, you know, every third year they are going to get immunized. I'd like to see second and third year, what the heck.

But if there is something that goes on the label about history of wheezing, then I would like to see some pretty in-depth studies on how well that is actually being ascertained. And follow it up in actual pediatric practices.

ACTING CHAIR MODLIN: Okay.

Mr. Wharton?

MEMBER WHARTON: Yes, I'd support the suggestions that have already been made.

The thing I'm most puzzled by is the safety profile that has been reported. And would like to have some better understanding about underlying pathogenesis. That seems to me to be the most critical thing here.

ACTING CHAIR MODLIN: Dr. Self?

MEMBER SELF: I think it looks fine. And I agree with some of the other comments.

ACTING CHAIR MODLIN: Dr. Jackson?

MEMBER JACKSON: Well, for this particular vaccine, if it is not restricted to people with any history of wheezing, to attempt to assess the safety in that group on the basis of data available from HMO systems, for example, is going to be difficult.

So we may want to consider having a subset in which, you know, telephone survey information is collected prospectively. Or something like that. Because some of these or many of these events would not necessarily come to medical attention so it can't be

ascertained in that manner.

And then I would say the majority of children in this age group who are getting their first dose of flu vaccine only get one dose instead of the recommended two. And so it would be nice to have some more information about what happens after only a single dose.

ACTING CHAIR MODLIN: All right.

Dr. Farley?

MEMBER FARLEY: I agree with all these suggestions.

A couple of other thoughts. In terms of the follow up, it might be as important to dictate not as much the size and number of people that are followed but making sure that it covers -- spans a number of flu seasons since not only the flu match and mismatch and such things but also other circulating viruses, if there is a co-infection come into the issue, if there is a big RSV year versus others, and those sorts

of things. So following it over a number of seasons as much as the volume of people that are followed.

And also I'm aware of vaccine effectiveness studies for the TIV vaccine in young children going on sponsored by CDC currently. And there may be ways to sort of partner with other organizations that might be willing to look at not only vaccine effectiveness in real life use, whether they get one dose or two, and those sorts of things but also could that be linked to some of the signal questions of safety signals as well?

ACTING CHAIR MODLIN: Dr. Daum?

MEMBER DAUM: So I think the only thing I would say that hasn't been said before is that the focus of the discussion has been concerned potentially about 12- to 23-month-old children. And I think there is a low level of anxiety about 24-month-old children and beyond.

And so I would like to see something extra done in this age group and focused on them. I don't know quite what to say or how to do it but I'd certainly be interested in hospitalizations and medically-significant episodes of wheezing after it should it be licensed in this age group.

So perhaps FDA and the company can work together to try to figure out how to do that. But I think those are important data.

In fact, I would go as far as to suggest that the Advisory Committee hear the results of that assessment on an ongoing basis.

ACTING CHAIR MODLIN: Thank you.

Dr. McIinnis?

MEMBER McINNES: I have nothing to add.

ACTING CHAIR MODLIN: Okay.

Dr. LaRussa?

MEMBER LaRUSSA: I agree with all the other comments. I would just say that if

the FDA does not approve the under 24 months and if studies continue in the six to 11 month age group, that six to 11 and 12 to 23 be stratified. And, if possible, powered to look at hospitalizations.

And I would be particularly interested in interaction with RSV and potentially power flu to see if you could sort of get a handle on what is going on with these categories that don't quite make a lot of sense for hospitalizations.

ACTING CHAIR MODLIN: Thanks.

I'd like to support each of the last two comments from both Drs. Daum and LaRussa. I think that a focused study on kids, not 12 to 23 months but six to 23 months, would be very useful, focused not only on trying to capture much better understanding of the safety issues and the pathophysiology behind the wheezing that is observed, but I think also getting a much better assessment of what the risk/benefit

ratio in that age group would be would be extremely helpful.

And I think would be very, very important for long-term usefulness of this vaccine.

Before we close, are there any other comments?

Norm, do you want to have the last word? Again, you invited us all.

DR. N. BAYLOR: Well, it will be very brief because it will be thank you.

ACTING CHAIR MODLIN: Okay. Thanks.

I wanted to thank everyone. We will break for lunch and we will start up again at two-thirty sharp.

(Whereupon, the foregoing matter went off the record at 1:30 p.m. to be reconvened in the afternoon at 2:30 p.m.)

ACTING CHAIR MODLIN: Good afternoon. By rough count, we have a quorum. So we will continue with this afternoon's

session.

The next item on the agenda will be a brief update on influenza strain selection. Obviously this is the focus of the meeting that this Committee had the last time. And this will be a brief update by Dr. Klimov.

COMMITTEE UPDATE: INFLUENZA STRAIN SELECTION FOR THE 2007 - 2008 INFLUENZA SEASON

INFLUENZA STRAIN SELECTION UPDATE

DR. KLIMOV: Good afternoon. And thank you for the opportunity come and talk today a little bit in the situation, the current situation, with the H3 component only.

As far as I recall, it's actually the very first time when we were asked to provide some follow-up information. And most of you know that vaccine strain selection is always a compromise between companies pushing us to make recommendations or to make new recommendations early. And the surveillance,

which meets in February, when the vaccine recommendation was made just in the middle of the season and would like to have more data to come.

So oh, my God. I'm sorry about that.

(Laughter.)

DR. KLIMOV: I didn't expect that this was so small. But, anyway, I will explain what is this. So this is the evolutionary 34H3 hemoagglutinin. And this is current vaccine strain A Wisconsin 67 2006. And you have nothing but just to trust me that recent H3 influenza virus or genetically most recent ones fall into two genetic subgroups.

One group is called Nepal 921-like viruses. And another group is called Brisbane 9 2006-like viruses. So that's essentially what the three are supposed to show.

And this is Brisbane. This is

Nepal. And this is one of the viruses which we first noticed that has some differences, so called Canada 1212. I am sorry that I expected that, actually, these sort of handouts were sent out about a month ago to the Committee. So maybe the Committee has this handout.

And the conclusion, it's about the same we had on February, end of February and during the VRBPAC meeting. There are two major genetic groups of the hemoagglutinin of H3 viruses: Brisbane 9-like. It's approximately right now 52 percent of H3 virus that belong to that group and 67, about two-thirds of those, viruses have reduced titers against ferret antiserum raised against the vaccines in Wisconsin 67. We will talk about this a little bit later.

We had several viruses, like three, I believe, from this group. They did not seem to do anything different from Wisconsin 67. We have one more. It happens

that it also has nine Wisconsin, but the Wisconsin 3 2007.

And there is Bucher who is responsible for preparing reassortants, working on the reassortant of this specific new virus with PR8, you know, the donor of high growth ability. So we will see what kind of characteristics this reassortant will have.

And the Nepal 921 2006 virus actually is a group which is more antigenically different from current Wisconsin 67 2006 virus. Approximately 46 percent global is the same approximately in the United States of recent viruses that belong to this Nepal group.

Sixty-six percent again, about two-thirds of viruses, have reduced titers against Wisconsin 67 vaccine strain. We have only one egg isolate so far, a Nepal 921 2006. And we have the reassortant prepared from this virus. And I will talk a little

bit about the antigenic properties of these viruses in a minute from now.

But this is just most updated, what we call frequency tables. So you can see that we have only about a third of viruses circulating right now antigenically similar to Wisconsin 67, but about two-thirds of viruses antigenically ware low to Wisconsin.

But please take into account that we don't know honestly. And it is very difficult to evaluate what percentage of those viruses are just so-called low aerate viruses, the viruses which do not bind to antibodies properly.

So antigenically I am going to show you a couple of tables. And here we have Wisconsin vaccine strain and Wisconsin reassortant. So this is wild type virus antisera obtained from these.

And just to remind you, we consider virus as antigenically different

when they have fourfold or higher difference between the homologous titer and the test virus titer.

So in this particular case, for example, you can see that homologous titer for Wisconsin wild type virus is 1,280, for Nepal is 640. For Brisbane, it's 2,560. So any titer above the homologous is considered to be the same as homologous titer.

So, I mean, in this sense, you see that we do not see actually clear antigenic difference between Wisconsin 67 and is a Nepal or Brisbane virus.

If you look at the Nepal antiserum raised against Nepal -- and this is Nepal wild type and Nepal reassortant. You can see that those viruses, both antigens have homologous titer 640. And they react with the same titer with Wisconsin. So, again, if you take Nepal or its reassortant, there is no twofold difference, neither this way nor that way.

At the same time, we do see that the Canada 1212 virus, which is, unfortunately for us, cell-grown virus, does show fourfold difference from Wisconsin. So it looks like at least one way is antigenic variant.

Also, if you compare to what extent Wisconsin and Nepal are what we call covering most recent viruses antigenically, Nepal does it a little bit better, not perfect, a little bit better, but not more than just a little bit better.

This is more recent table. And I believe that here we have antisera raised against not only Nepal wild type but also Nepal reassortant prepared by Doris Bucher.

Again, you know, we do not see essential difference between Wisconsin and the Nepal viruses. And even, you know, wild type seems to do a pretty good job covering the most recent viruses. That doesn't seem to be the case for the antiserum raised the

reassortant. It does not behave perfectly.

During the previous VRBPAC meeting, we also were talking about the need in performing so-called neutralization tests versus just hemoagglutination tests. And the group in our branch, they performed -- I will show you later -- another table which is a little bit better. I will show you they performed such a test. And this table -- again I'm sorry it's probably not very well-sealed.

This is a comparison between HI titers and microneutralization titers. Use of several different recent viruses, in this case we have Brisbane, Nepal, Canada 1212, and another virus from the Nepal group, and cell-grown virus.

So the titers, let's concentration mostly on the test vaccination genetic meaning titers. The titers were neutralization are higher than the titers when you use hemoagglutination. This is not

a big surprise.

But also we can see that there is not much difference in the pattern between HI data and the neutralization data when we look at the paired sera obtained from adults, healthy adults, immunized with Wisconsin 67. But if we look at the sera from elderly people vaccinated with this, you can see that there is pretty dramatic reduction in HI titers post-vaccination, mean titers, as in HI tests, as in the microneutralization tests.

So hopefully this table may be a little bit larger because it represents only neutralization data. We performed another experiment with more broader spectrum of viruses from both Brisbane and Nepal group.

And, again, essentially except with Canada 1212, the reduction in the post-vaccination mean titers for most of the viruses within the adult, with a group of adults, was not dramatical, but it is quite

significant when you compare titers using pediatric sera, sera obtained from kids immunized with Wisconsin 67 or if you take sera taken from elderly people.

So general conclusions, two major genetic groups right now of the H3 hemoagglutinin and Nepal-like and Brisbane-like, HI tests using ferret antisera to the A Nepal 921 '06 are certain virus -- once again, this is the only egg-grown virus which we have from that group right now -- indicates that this virus is not a superior vaccine candidate when compared with the Wisconsin vaccine strain.

Also, post-protection ferret antisera to Nepal and Canada cover recent H3N2 viruses somewhat better than antisera to Wisconsin. There are no reciprocal two-way differences in antibody titers when those three viruses are compared.

Microneutralization tests conducted with post-infection ferret antisera

-- I didn't present those data -- also indicate that only a one-way difference can be absorption, not the two-way reciprocal difference could be detected between Wisconsin-like and Nepal-like viruses. And when I say, "Nepal-like," essentially it means Nepal and Brisbane-like viruses.

Microneutralization titers with human post-vaccination sera are higher than HI titers, which was expected, but there is no consistent reduction in the serum antibodies from the U.S. adults when compared with homologous titer using the Wisconsin strain if you use the Nepal-like viruses for testing.

There are, however, some obvious reductions when the sera from elderly or children were tested. And there is more than four-fold reduction in the neutralization tests for elderly or kids.

Overall conclusion. We cannot detect a reciprocal two-way difference in the

HI or microneutralization titers for the Nepal-like viruses in ferret antisera and antisera made using the Nepal virus.

And Nepal virus is not superior in the current recent viruses. Therefore, the results are consistent with the February decision to recommend the Wisconsin 67 2005 to be included in the 2007-2008 influenza season vaccine.

Thank you.

ACTING CHAIR MODLIN: Thanks, Dr. Klimov.

Are there questions for Dr. Klimov? There is a nice follow-up to a very sort of handering discussion that we had at the meeting just a couple of months ago.

(No response.)

ACTING CHAIR MODLIN: I guess not. Thank you very much. We appreciate you coming up to give us this follow-up.

We will continue on to a different part of the agenda, which will be a

responsibility that this Committee has to provide an overview of the Laboratory of Bacterial Polysaccharides in the Laboratory of Enteric and Sexually Transmitted Diseases of the Division of Bacterial Parasitic and Allergenic Products from the OVRR.

I guess we will start out with an overview of the laboratory by Dr. Vann. Dr. Vann, thank you. TOPIC 2: OVERVIEW OF LABORATORY OF BACTERIAL POLYSACCHARIDES/LABORATORY OF ENTERIC & SEXUALLY TRANSMITTED DISEASES, DIVISION OF BACTERIAL PARASITIC & ALLERGENIC PRODUCTS, OFFICE OF VACCINES RESEARCH AND REVIEW, CBER OVERVIEW OF LABORATORY OF BACTERIAL POLYSACCHARIDES

DR. VANN: Okay. I will present an overview of the Laboratory of Bacterial Polysaccharides. If you have specific questions about research programs that I cover here, the PIs that manage those programs are in the audience. And you can

direct them to them.

The Laboratory of Bacterial Polysaccharides investigates the biochemistry, biology, chemistry, and immunology of virulence factors of encapsulated bacteria. These virulence factors include capsular polysaccharides, lipopolysaccharides, and automembrane proteins.

The laboratory has review responsibility for submissions related to polysaccharide and polysaccharide conjugate vaccines. In addition to some noncapsular emitigens of encapsulated pathogens.

Here is a brief chronology of the Laboratory of Bacterial Polysaccharides since its last site visit. It was last site visited in 2002. In 2004, Dr. Carl Frasch, who had been lab chief for many years, stepped down as lab chief. And Dr. Milan Blake, who had just become deputy director of the division, became acting lab chief.

In 2006, I, Willie Vann, was appointed lab chief. And with that, there was a major reorganization of the Laboratory of Bacterial Polysaccharides.

The glycobiology group, which was part of my first group in the Laboratory of Bacterial Toxins, joined the Laboratory of Bacterial Polysaccharides.

At the same time, the Laboratory of Biophysics was actually merged. Part of it was merged. The NMR group and the mass spectrometry group were merged into Laboratory of Polysaccharides.

This resulted in this organization chart here, where we now have five groups: structural biology; analytical biochemistry; glycobiology; cellular immunology; pathogenesis; and a new group, vaccine structure.

The current research staff are as follows. So in the structural biology group, the PI there is Dr. Daron Freedberg. He has

a postdoctoral fellow and Scott Norris, who is an NMR spectroscopist.

Analytical biochemistry is headed by Dr. Tsai, who actually also now has responsibility for lot release. And he has two assistants.

Cellular immunology, Dr. Akkoyunlu is the PI there. He has a postdoctoral fellow and a technician.

The glycobiology group is more complicated because we merged some groups that were already in the bacterial polysaccharides with the glycobiology group from toxins.

So glycobiology group now has three subsections: conjugate chemistry, biochemistry, and epidemiology. The conjugate chemistry is managed by Dr. Robert Lee, who is a staff scientist in the group. And the molecular epidemiology is managed by Margaret Bash, who is a medical officer in the group. And these are the people who were

transferred from toxins.

Now we have a new box, a new group: vaccine structure. Dr. John Cipollo has joined us as the PI for that in April. And he joined us since the last site visit. We are currently recruiting him a spectrometrist and a postdoctoral fellow for him.

The areas of research conducted in the Laboratory of Bacterial Polysaccharides include structure and confirmation of capsular polysaccharides, the biosynthesis of capsular polysaccharides, the role of noncapsular antigens and protection, the interaction of capsular polysaccharides with the immune system, and the development of methodologies for the analysis of conjugate vaccines.

The relevance of this research program to the mission, the Laboratory of Bacterial Polysaccharides has regulatory responsibility for vaccines against

encapsulated bacteria and products containing bacterial polysaccharides.

The overall goal of the research program is to understand the virulence factors that are components of these vaccines against bacterial pathogens. The research program is directed toward understanding the physical, chemical, and immunological properties of bacterial polysaccharides, and polysaccharide conjugate vaccines.

This knowledge and expertise gained in this research endeavor provide us with a basis for decisions regulated to review of manufacturing, purity, potency, and safety of carbohydrate-containing vaccines.

I will in the next few minutes outline a few of the accomplishments of the laboratory since the last site visit, research complements, and some regulatory complements.

One of them is the development of an efficient method for meningococcal

conjugate vaccine synthesis. This was part of a project from the Meningitis Vaccine Project of the WHO. They needed a vaccine that was actually cheap to produce for the Third World. And it just so happened that the research that was ongoing in the laboratory sort of fit that bill.

The way that project is organized is outlined in this slide. This project was originally managed by Dr. Carl Frasch at CBER and Mark LaForce of Meningitis Vaccine Project. It was funded by the Gates Foundation through PATH.

The technology for the synthesis of the conjugate vaccine was developed by Robert Lee in the Laboratory of Bacterial Polysaccharides. This conjugate technology was then transferred to the Serum Institute of India, which manufactured the vaccine to be used in the clinical trial.

The serology is actually also being analyzed by the CDC and also by Dr.

Margaret Bash in the Laboratory of Bacterial Polysaccharides. There are other people who contributed to this project, who include Daron Freedberg and Scott Norris in the structural biology group.

The analytical biochemistry group has developed LGLC methods for quantitation of phosphate and acetate in polysaccharide vaccines. They have characterized the lgtH gene cluster Neisseria LOS biosynthesis and have demonstrated that the LOS of the comensal Neisseria polysaccharea is similar to the LOS of the meningococcal pathogen.

The molecular epidemiology group under Dr. Margaret Bash has developed and applied molecular methods to the study the automembrane protein PorB diversity. It was demonstrated that horizontal genetic exchange predominates persistent of PorB variable regions. Sequences, types indicates that diversification is constrained and has identified survival of antigens associated

with PorB types.

The relevance, this is relevant to the development and evaluation of broad protective automembrane protein vaccines where polysaccharide vaccines may not be effective.

The cellular immunology group has concentrated on two areas: one, the interaction of polysaccharides with the innate immune system, and the modulation of the vamped April system molecules with microbial products.

I have shown that Neisseria meningitis group C polysaccharide binding and the CD14 and LBP, binding to like LPS, mediates cell activation. One very significant observation is that decreased expression of TACI on newborn mouse B-cells may be responsible for the impaired immune response of newborns to polysaccharides. I've shown that total receptor antagonists CpG, DNA, and LPS strongly upgrade/regulate

TACI expression on B-cells.

The structural biology group, headed by Dr. Daron Freedberg, has taken two approaches. Their primary interest is in confirmation of carbohydrates; that is, what antigens our antibodies bind to and what antigens does the host see.

So one thing they have done is actually looked at the structure of polysaccharides on the cell using stabilize isotope NMR and shown that the structure of a polycyclic acid similar to Mening B is the same as the solution structure that is present in the vaccine.

They have also developed methods to look at smaller molecules using newer NMR methods and using sucrose as their model system have shown that this actually works to distinguish between various confirmations of sucrose. This can then later be translated to larger polysaccharides.

We have license product

responsibility for a number of polysaccharide and conjugate vaccines, as illustrated in this slide, Pneumo 23 valent meningococcal tetravalent polysaccharide vaccine typhoid VI, and then several conjugate vaccines, many of which I think this Committee has seen.

With that, we have responsibility for lot release. And that, as I mentioned before, is responsibility of Dr. Tsai. Theresa Wang, who works in his lab, assays some of these lots, a fraction of these lots, for tests, a fraction of these lots. But, despite whether all of these lots are tested, all of the protocols, which amount to about 400 per year, are reviewed by this group.

Some regulatory accomplishments during this review period since the last site visit include licensing of the tetravalent meningococcal conjugate diphtheria toxoid vaccine, ACYW135. The trade name is Menacra.

And there have also been significant changes in the analytical

methodology used for lot release, in some cases going from normal gravity fed to HBLC for size determination and using NMR for identity tests.

Other regulatory accomplishments include the review of numerous INDs, BLAs, and BLA supplements. We have participated in international policy working groups.

And one of our things is to distribute. We have distributed reference materials for assays for haemophilus and pneumococcal antibodies.

Thank you.

ACTING CHAIR MODLIN: Questions?

QUESTIONS/CLARIFICATIONS

MEMBER GELLIN: Yes. Thanks. You outlined a lot of your accomplishments. I'm curious to know about how you go about setting your research agenda. Given the millions of things that you could possibly look at, how do you decide on the ones that you would actually look at?

DR. VANN: Okay. What we don't do is we don't direct research at every little problem. What we try to do is actually develop a line of expertise that can address a problem.

So that, for example, if I have someone working on confirmation, using NMR, now, that person actually has a lot of expertise that comes along with that. So that if we do have a problem where we need to explain something about a composition using NMR, that person can address it. But his research is not going after doing that. He has a research program that is rather focused.

So, to answer where does the direction come from, what problem to work on, that is, as I think it should be, from investigator-initiated.

ACTING CHAIR MODLIN: Kathy Carbone?

DR. CARBONE: Hi. I'm the

Associate Director of Research for CBER. Over there is Mike Brennan, who is the associate for the office. I think Willie is -- Dr. Vann. Sorry, Willie.

DR. VANN: Yes.

DR. CARBONE: We are always informal with our first names.

He is exactly right in that we obviously have a limited amount of resources and time and can't address every problem. He is also exactly right that by having people working in real science, we have the expertise to be flexible and move very rapidly.

However, something that we have rolled out at a high level that Dr. Vann may not be intimately aware of yet because it is still in draft form is the formal research management process at CBER that actually includes investigator comments because, after all, these investigators, the people doing the review, have their feet on the ground.

And they know what problems are rolling down the pike.

However, the way it is done is a now formal process identifying priorities based on a whole range of items. And, in fact, you will be hearing as the Advisory Committee a report on this from Dr. Brennan coming up shortly with more detail. So I don't want to take a lot of time now.

ACTING CHAIR MODLIN: Right.

DR. CARBONE: But there is a process. And it works, CBER's as well as the office's translation of the main priorities for CBER and then, of course, the investigators' contributions from what they see.

So there really is a formal process now, but I think the investigators are pretty good at identifying problems. And they have to get it right.

DR. VANN: Yes.

ACTING CHAIR MODLIN: Thanks.

Dr. McInnes?

MEMBER McINNES: Dr. Vann, it is so nice to hear the summary and the update from the lab because I think if you look at the products for which you have license product responsibility, they are some of the amazing success stories of the last 18-20 years all the way now through ongoing successes.

And I think this was a wonderful model for how CBER scientists' role was just so complementary and value added to this whole product development agenda for these largely focused on capsular polysaccharide, you know, technologies, et cetera, all the way from production of reagents to testing to being an active research partner with pharma, academia.

It was really a model, among many other models at CBER, actually. But this particular group does have some of those terrific success stories, particularly for

pediatric infectious diseases.

So thank you. I enjoyed the update on the lab.

DR. VANN: Good. I can add one thing to that to illustrate. Robert Lee was working on pneumococcal conjugate vaccines. And it wasn't because he got some directive to actually do that. It's because he was interested in that.

And what happened is MVP needed a vaccine for Mening A. Now, he had the expertise, and he knew how to do that with pneumococcal vaccine. So he simply translated it to Mening A. Now we have a vaccine that is actually in clinical trial.

So that is what I mean by investigator-initiated who actually has the expertise. He has a focused direction. And when it is needed, he can apply it. But he doesn't go and direct it based on a little problem here, here, and there.

ACTING CHAIR MODLIN: Dr. Daum,

this is right up your alley.

MEMBER DAUM: I don't know. I'll leave that one alone. I think that I haven't been close to the situation in several years. And so I could be curious to hear from Willie or from Kathy how the funding for the research situation is going.

I know the last time I looked in on this window, it was a terrible problem with very limited sources. And you came away with the feeling that this wonderful research that Dr. McInnes talked about was hampered by a resource issue.

I hope the problem is completely solved and gone away and you are not dealing with it anymore, but I doubt that is so. And I wondered if you would say a little bit about whether it has ameliorated or improved a little bit because it's, as always, very important work and we would like to hear more of it.

ACTING CHAIR MODLIN: Dr. Baylor?

DR. N. BAYLOR: I'll speak, Bob. And I'll speak for the office. And than Kathy can follow up for CBER.

The issue has not gone away, but we have not gone away either. And I think it is sort of we have been able to leverage some resources. We have been very successful -- and I should take the "we" out and say the investigators -- very successful at really obtaining funds from extramurally primarily from other government agencies, such as the NIH, MVPO. And these have really helped us out quite a bit.

And then there are also other initiatives within the Department, such as the pandemic influenza. We are able to get resources from that. And that can help build an infrastructure, even though it is related to pandemic. That does contribute to our infrastructure.

So I cannot say that we have solved the problem completely, but we are in

a position that we can continue. We try to continue to do as much as we can and try to continue to leverage some of those resources.

That's the good news. Maybe not so good news is those extramural funds, especially the limited funds that we can obtain. Those are not guaranteed. So we, again, haven't solved the problem permanently, but we are still able to contribute and get our mission done.

MEMBER DAUM: Thanks, Norman. Can you now directly apply for NIH support or does it still have to be through a PI from external sources?

DR. CARBONE: We've been working on this, both at CBER and agency-wide. It all is based on a DHHS and NIH policy of being able to move funds from one agency to another within DHHS.

And NIH has a policy, which is actually quite clear, that states that they do not fund other federal investigators

except under specific circumstances, which include unique expertise, no one else in the country can do it, et cetera.

And we have had some meetings with some of the administrators at the NIAID institute to talk to them about that policy and how we might be able to meet it. But I think to get to the actual facts of the matter, generally we can't and don't apply as PIs.

We have been successful in the past applying as co-investigators, although there have been cases where the funding has been pulled specifically because we are federal scientists. I know of three grants last year that were not, our portion was not, funded because of that issue.

Now, that said, NIH obviously has budget challenges now as well. There are external investigators that are dependent on them for literally their livelihoods for those extramural funds. And so I can respect

NIH has a problem with balancing those concerns.

And so I think the sum total is what Dr. Baylor said, which is ideally it would be best to have a reasonable amount of intramural support, well-managed, well-focused, and value-added, and not have to rely on outside sources of funding.

I think this is also true of some of the workshops we put on where we opened up the leverage with other agencies. And in time we can do that, but it would be much better to have these funds and resources ourselves to be able to address some of these scientific issues that may be very specific to the FDA.

ACTING CHAIR MODLIN: Thank you. Other questions, comments?

(No response.)

ACTING CHAIR MODLIN: If not, thank you very much, Dr. Vann.

DR. VANN: Okay.

ACTING CHAIR MODLIN: We will move on to the next presentation, which will be an overview of the Laboratory of Enteric and Sexually Transmitted Diseases. And that will be Dr. Dennis Kopecko.

OVERVIEW OF LABORATORY OF ENTERIC & SEXUALLY TRANSMITTED DISEASES

DR. KOPECKO: Good afternoon. I'm going to be presenting a little bit of information that is directed toward Dr. Daum's comments about funding to try to keep this discussion going a little bit.

It is with great pleasure that I take this opportunity to introduce the Lab of Enteric and Sexually Transmitted Diseases over the next few minutes, to discuss who we are and the general areas that we work in and the products that we are involved in regulating.

In the Lab of Enteric and Sexually Transmitted Diseases, we are divided up into three groups: molecular pathogenesis group,

a genetic regulation group, and immune mechanisms group.

And we integrate our research fairly well. We then carry out studies on mechanisms of pathogenesis, gene expression and control, immune mechanisms, and various aspects that will lead to advances, I hope, in vaccine development. And we use all of this information to help us in our regulatory oversight duties.

This is the organizational chart of the lab at the time of the site visit back in November. I head up the molecular pathogenesis section. I have a series of scientists. Siba Bhattacharya is a regulatory scientist who spends 80 to 100 percent of his time doing regulatory work, so not much for research; DeQi Xu, long-time research fellow, senior scientists; Dr. Lan Hu, also a senior scientist working in the lab. Tint Wai came within the last couple of years as a research assistant. Jim McDaniel

is a long-time research assistant who has been during the entire review period. Kansuke Shima came last summer from Osaka. And Yanping Wu started about two years ago working with us and just recently left.

Within the gene regulation group, headed up by Dr. Scott Stibitz, during this review period, he has worked with his research assistant, Mei-Shin Yang; with Wendy Carr, who just recently left us; and much of this review period, Phil Boucher, who left about a year ago.

And the new mechanisms group, which Richard Walker, Dick Walker, is acting head. Manuel Osorio is an immunologist who has been initiating a series of new studies and has worked during this past review period with Michelle Bray, who left us back in August, and now has been replaced with Suneil Singh in December.

So there are a couple of points I want to make. It's a fluid lab situation.

The size of the groups has changed over the review period now. I'll focus on that in a minute.

Also, these three or five positions that are blocked in yellow are Oak Ridge fellows who are supported by outside funding. So almost half of our lab is outside funded or outside supported. That certainly has changed over the 13 years that I have been here.

Our lab began in 1994, when I moved over from the Walter Reed Army Institute of Research. It was established to review an increasing number of enteric disease products and an onslaught of expected STD products that has never actually occurred.

Our mission, then, is to conduct basic and applied research. And I mentioned that we work on molecular bases of pathogenesis, host immune responses to infection, and developing models to measure

vaccine safety, immunogenicity, and efficacy.

And we try to attack unique problems in terms of enteric vaccine development. And we utilize this knowledge base to enhance our review of manufacturing as well as product safety and efficacy. Our last program review was carried out about four years ago.

Now, in order to give you a better appreciation for the research that we are doing, I thought I would take a minute and explain the types of products that we regulate to tell you the breadth of experience that we need in order to regulate these products.

So obviously, as all other labs were involved in reviewing INDs and BLAs for products in the bacterial enteric area, urinary tract infection, sexually transmitted disease, and a variety of other products that I will mention below, typically we cover the standard enteric pathogens, shigella,

salmonella, pathogenic E. colis, Campylobacter, vibrio cholerae, Helicobacter pylori, more recently hookworm; the use of live attenuated bacteria as vaccine vectors for multivalent antigen delivery; the use of salmonella in anti-cancer therapies to target tumors; quite a number of urinary tract pathogens; a variety of probiotic products that are now being used for specific medical indications.

And we call these live biotherapeutic products aimed at treating various cancers, inflammatory bowel disease, cystic fibrosis, and a variety of other conditions; use of L. asparaginase to treat acute lymphocytic leukemia, use of bacteriophages or bovine and chicken-derived immunoglobulin concentrates for therapeutic use, and genetic hybrid plant vaccines. This is not all-inclusive but covers most of the products.

And these products involve oral

administration, parenteral, intrarectal, intravaginal, intranasal, transcutaneous routes, and the use of new adjuvants. So you can see it covers a pretty board area.

I won't get into the total number of products, but in terms of review time, Dr. Stibitz and I are the PIs with longstanding experience. And obviously we put in more effort in review. So both of us have about 50 percent of our time spent on reviewing. And that fluctuates, obviously, depending upon the regulatory workload. Sometimes it's much closer to 75 percent.

The new investigators, Wendy Carr, Manuel Osorio, are establishing research programs and learning regulatory work and have 25 to 30 percent effort. And I mentioned Dr. Bhattacharya has a larger effort in review.

As far as a couple of factors that affect us are the change in the number of personnel to carry out research, which is

influenced by budget. So the molecular pathogenesis group during this review period increased from two to seven, mainly as a result of some special NIH biodefense project funding.

The gene regulation group declined from five to three and is now back on the increase again.

The STD group was abolished due to the lack of a lot of STD product activity and the departure of Carolyn Deal. And the immune mechanisms group has just begun over this past four-year period.

I wanted to point out that the FDA intramural research budget has continued its decrease. And in this last four-year period, it's reduced in half to what it was at the beginning of the period.

On a per capita basis, although we're changing that, that equates to about $7,500 per capita, not a lot of money. Fortunately, outsider supporters replaced the

intramural budget decline and actually even more than replaced that, but there is not only the problem of lack of internal funding consistency. There's a limited number of outside sources that we can go to for funding. We can't apply directly to NIH, only for special programs, which has already been raised as an issue.

So having said that, let's get into the research. I think all of you are aware that enteric bacterial diseases are a significant problem, causing more than 350 million episodes of diarrhea a year in the U.S., killing a couple of million children a year worldwide. And there is limited data on pathogenesis and immune responses that have limited the development of more enteric vaccine products. And, in fact, we only have one license product now, Ty21a, in our group, although the VI capsular polysaccharide is the second enteric disease-directed product, the second licensed.

Our research falls under DHHS and FDA priorities. And it's encapsulated in these two program areas: Enteric bacterial pathogens, improving safety and efficacy of combination vaccines for diarrheal disease and select agents; and then bacterial vaccine safety biomarkers of virulence attenuation and Bordetella pertussis and anthrax bacteria.

So I am going to summarize some of the approaches and projects that we have worked on during the last four years in sort of broad summary statements. And if you have further questions, I would be happy to answer them. And I am going to divide these by the sections.

So molecular pathogenesis section during this review period has focused mainly on two large projects utilizing salmonella typhi Ty21a, the only licensed enteric vaccine product, to study its safety and the ability of it to express multiple antigens,

which is a goal of many different enteric vaccines currently under development; and, secondly, to continue our studies on pathogenesis and immune responses to Campylobacter jejune infection.

And there are a number of minor research projects. One, if you have looked at the research summary, involves the use of salmonella to target tumors. I don't have time to talk about the amount of projects, but the key collaborators have been very important in providing not only research support but financial support to finish some of these minor studies.

In the case of using salmonella typhi or studying salmonella typhi as a vector platform system, there have been three overall goals in this review period. The first is to define the key attenuating features of Ty21a.

This vaccine was developed 25 years ago using random chemical mutagenesis.

And it's thought to have multiple mutations. And there is some data to suggest that the gallapolymerase mutation and the VI capsule are not the essential attenuating mutations.

So we have started a genomic sequencing and now have completed 98 percent of the genome. We found 500 single nucleotide position changes relative to the parent Ty2. We are trying to combine that data with micro array analyses to be able to find what the key attenuating features for the strain are.

That information will not only tell us a little bit more about the safety of Ty21a. It can be applied to other vaccines that have those same genes.

One problem that is true for most vaccines but certainly for enteric vaccines is to take them out to the developing world, where they are going to be very useful, one needs to have or would like to have a temperature-stabilized product that you don't

have to refrigerate.

So, fortunately, through a series of circumstances, we have been able to set up a collaboration under an NIAID-supported SBIR grant with Aridis Pharmaceuticals using Ty21a, which is off patent now, and have been able to formulate some temperature-stable preparations that survived for 3 months at 37 degrees, showing good promise for being able to translate some of this technology with many different vaccines out to developing countries.

We are also looking at new delivery systems, like rapidly dissolvable wafers. And we have also carried out a fair amount of work on the expression of multiple LPS antigens as well as more simple protein antigens, like anthrax PA, in Ty21a.

In Campylobacter, our overall goals during this period were to examine C. jejune attachment invasion and specific translocation or exocytosis events using

transmission and scanning EM.

We have also looked at a series of host signal transduction pathways that are intimately involved in the ability of host cells to take up C. jejune.

And we have looked at the interaction of C. jejune with human dendritic cells for cytokine and chemokine synthesis and their involvement in inflammation and colitis.

For the immune mechanism section, the new directions that they have taken are to evaluate various approaches for achieving mucosal immunization, focusing heavily on whole cell vaccines.

They have been studying various methods for inactivating enteric bacteria, trying to optimize those that retain immunogenicity, looking at a variety of different antigen delivery systems, transcutaneous, bacterial ghost, or mucosally delivered whole cells, to see how they can

achieve optimum immunogenicity.

Also, Manuel Osorio and his group have been heavily involved in developing animal models for evaluating vaccine efficacy of typhoid, shigella vaccines, anthrax vaccines, and very recently have set up a very nice in vivo imaging system that might be useful for evaluating ETEC vaccines. And there isn't currently a good animal system for ETEC.

In the third section, the gene regulation section headed up by Scott Stibitz, he has had a longstanding study on virulence gene regulation, studying the B. pertussis II component regulatory system BvgA and S. More recently he has received funding to develop genetic tools for the analysis of manipulation of B. anthraces.

Under the first project, he has continued his molecular studies to try to understand how this BvgA activator bounds to promoters and varies the level of expression.

So he has looked at binding to eight different promoters using a high resolution mapping to determine how BvgA binds to RNA polymerase and to the promoter to effect these different levels of gene expression. And he hopes to continue these using genetic studies to elucidate those critical interactions that allow for maximal gene expression.

He has also been involved in his group in developing genetic tools in B. pertussis, a powerful allelic exchange system for manipulation of unmarked B. pertussis strains that allow their use in animal studies.

And they have created by illuminescence B. pertussis that now can be followed in an in vivo animal infection model and a mouse aerosol challenge. They find that they can follow individual mice. They get a characteristic upper respiratory infection that begins in the nose, and it's

followed, then, by growth in the lungs and the trachea.

And hopefully using this model, they can then utilize some of the key mutations that have been developed in novel virulence genes and regulatory phenotypes to see how those genes affect the disease process.

And, finally, the second project, they have been developing allelic exchange procedures for use in B. anthraces. They have constructed 70 targeted mutants in B. anthraces and hope to continue to develop new additional tools of various types of vector, promoter assay vectors, transpose on delivery vectors, applying these tools in a genomic search for new virulence genes.

And also this portion of the project received funding from MARCE. And then a special CBER-NIAID funds this last approach of looking for the underlying causes in B. anthraces that lead to the instability

of rPA anthrax in the current recombinant vaccine.

So that is a summary of the lab. Thank you very much for your attention.

ACTING CHAIR MODLIN: Thanks, Dr. Kopecko.

QUESTIONS/CLARIFICATIONS

ACTING CHAIR MODLIN: Questions? Maybe I could ask. What is the issue of stability with the PA vaccine? I didn't realize there was one. Could you enlighten us a little bit more?

DR. KOPECKO: One of the issues is -- and I might let Scott Stibitz pick this up because this is his area of expertise -- proteases and the control of those proteases. Scott, do you want to more directly address that?

DR. STIBITZ: Yes. So initially the history of this project depends upon what the vaccine that had been selected for the strategic national stockpile was. Several

years ago when we initiated this project, that was a vaccine where rPA was purified from anthraces strains.

And since anthraces makes a number of secreted proteases, we had the ability to go in and knock those out genetically and create a protease-free strain. And we thought that that would impact positively on long-term stability.

Since that time, they have dropped that strain and are now using an rPA made in recombinant E. coli. However, it turns out that there are still significant stability issues. And I am not sure how much I can go into that but that appear to be intrinsic to the protein perhaps, unknown.

So we plan on approaching that in collaboration with our NMR colleagues and using genetic techniques to see if we can improve that situation and derive tools to examine it more rigorously.

ACTING CHAIR MODLIN: Thank you.

Phil, did you have a question?

MEMBER LaRUSSA: Yes. Just a thought. You know, I was thinking of areas of synergy between the two labs. And it came to mind that Campylobacter is at least epidemiologically linked to cases of Guillain-Barre syndrome.

And at least there is a signal of Guillain-Barre syndrome after Menacra vaccine. Whether it's real or not is another story. But it comes to mind that maybe the mechanism of development of Guillain-Barre might at least be similar in those two entities and whether you guys are thinking about looking at the immune response to Campylobacter and comparing it to Menacra and seeing if there is something you can learn there.

DR. KOPECKO: Actually, we haven't talked about that. My wife, who works on Campylobacter, is heavily involved in cloning and identifying the sugar transferase that

make the gangliocyte mimicry on the surface. So there are already approaches to try to knock out the essential genes and actually make a safe challenge strain that can be used to show protection with Campylobacter vaccines.

We are interested in that.

ACTING CHAIR MODLIN: Dr. Vann?

DR. VANN: Yes. I think one of the thoughts about Campylobacter and Guillain-Barre is molecular mimicry. And the life of polysaccharides of Campylobacter look like gangliocyte structures on the host. So you end up making antibodies to yourself with Campylobacter.

Menacra, that's a totally different case. I mean, we actually thought about that. And there are no structures, there are no carbohydrate structures, in there that actually resemble anything that is on the host. So it is probably either a statistical fluke or a different mechanism.

ACTING CHAIR MODLIN: Other questions or comments?

(No response.)

ACTING CHAIR MODLIN: If not, Dr. Kopecko, thank you very much. We certainly appreciate the update. I think we all enjoy, even at a superficial level, hearing what is going on scientifically.

OPEN PUBLIC HEARING

ACTING CHAIR MODLIN: I guess we need to ask if anyone would like to make a comment in the open public hearing session.

If not, I understand that we will now go into closed session. Why don't we take a one-minute break? And then we'll come back and hopefully be in closed session at that time.

And I understand that, Dr. Carbone, it is your responsibility to clear the room of those who aren't supposed to be here. Thanks.

(Whereupon, the foregoing matter

was concluded at 3:34 p.m.)