Docket 5

UNITED STATES OF AMERICA

FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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VACCINES AND RELATED BIOLOGICAL PRODUCTS

ADVISORY COMMITTEE

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93RD MEETING

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TUESDAY,

DECEMBER 17, 2002

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The Advisory Committee met at 8:30 a.m. in the Congressional Ballroom of the Bethesda Marriott, 5151 Pooks Hill Road, Bethesda, Maryland, Dr. Robert S. Daum, Chairman, presiding.

PRESENT:

ROBERT S. DAUM. Chairman

NANCY COX, Ph.D., Temporary Voting Member

MICHAEL DECKER, M.D., M.P.H., Non-Voting Industry Representative

PAMELA S. DIAZ, M.D., Member

KATHRYN EDWARDS, M.D., Temporary Voting Member

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PRESENT (Continued):

THEODORE EICKHOFF, M.D., Temporary Voting Member

WALTER L. FAGGETT, M.D., Member

BARBARA LOE FISHER, Consumer Representative

HOLLI HAMILTON, M.D., M.P.H., Temporary Voting Member

BRUCE GELLIN, M.D., Temporary Voting Member

JUDITH D. GOLDBERG, Sc.D., Member

SAMUEL L. KATZ, M.D., Member

DAVID M. MARKOVITZ, M.D., Member

MARTIN MYERS, M.D., Temporary Voting Member

GARY D. OVERTURF, M.D., Member

JULIE PARSONNET, M.D., Member

DIXIE SNIDER, JR., M.D., M.P.H., Temporary Voting Member

MARK STEINHOFF, M.D., Temporary Voting Member

DAVID S. STEPHENS, M.D., Member

FDA REPRESENTATIVES:

KATHRYN ZOON, M.D.

ROLAND LEVANDOWSKI, M.D.

KAREN MIDTHUNE, M.D.

ChrisANNA M. MINK, M.D.

DOUGLAS PRATT, M.D., M.P.H.

WASIMA RIDA, Ph.D.

SPONSOR REPRESENTATIVES:

ROBERT BELSHE, M.D.

KATHLEEN COELINGH, Ph.D.

EDWARD CONNOR, M.D.

ROBERT KOHBERGER, Ph.D.

PAUL MENDELMAN, M.D.

BRIAN MURPHY, M.D.

KRISTIN NICHOL, M.D., M.P.H.

JAMES YOUNG, Ph.D.

C O N T E N T S

P R O C E E D I N G S

(8:35 a.m.)

CHAIRMAN DAUM: Good morning and welcome to the meeting of the Vaccines and Related Biological Products Advisory Committee. Let me begin by asking everyone in this room to consider some personal noise hygiene measures at this moment and to please turn off all beepers, all cell phones or at least reduce them to a vibrating mode where no one will be disturbed by hearing them.

The second measure, usually the first, I'd like to turn the floor over to Dr. Sachs, Jody Sachs of the FDA, for administrative matters, including a conflict of interest statement.

Dr. Sachs.

DR. SACHS: Welcome to the 93rd meeting for the Vaccine and Related Biological Products Advisory Committee. I welcome the members, and thank you all for coming, and also I welcome the public.

I'd like to read a conflict of interest statement for the record.

The following announcement addresses the conflict of interest issue associated with the Vaccine and Related Biological Products Advisory

Committee meeting on December 17th, 2002.

The Director of the Center for Biologics Evaluation and Research has appointed Nancy Cox, Dr. Kathryn Edwards, Dr. Theodore Eickhoff, Dr. Bruce Gellin, Dr. Holli Hamilton, Dr. Martin Myers, and Dr. Dixie Snider and Dr. Mark Steinhoff as temporary voting members for this meeting.

To determine if any conflicts of interest existed, the agency reviewed the submitted agenda and all financial interests reported by the meeting participants. As a result of this review and based upon the FDA draft guidelines on disclosure and conflict of interest for special government employees participating in an FDA product specific advisory committee meeting, there were no meeting participants who required a waiver under 18 USC 208.

Dr. Diane Griffin, Peter Palese, Richard Whitley recused themselves from participating in this meeting.

We would like to note for the record that Dr. Michael Decker is participating in this meeting as a nonvoting industry representative acting on behalf of regulated industry. Dr. Decker's appointment is not subject to 18 USC 208.

He is employed by Aventis. In the event that the discussions involve specific products or firms not on the agenda and for which FDA's participants have a financial interest, the participants are reminded of the need to exclude themselves from the discussion. Their recusal will be noted for the public record.

With respect to all other meeting participants, we ask in the interest of fairness that you state your name and affiliation and any current or previous financial involvement with any firm whose product you wish to comment upon.

The following VRBPAC members will not be present today: Dr. Diane Griffin, Dr. Audrey Manley, Dr. Peter Palese, and Dr. Richard Whitley.

In your members' folder on the left-hand side there's a flyer that tells you at noon there are two restaurants that are open in the hotel available for lunch. So it's a little flyer and it shows you what two restaurants you can eat lunch at quickly.

And with that I'm happy to turn over the meeting to Dr. Daum, our Chair.

CHAIRMAN DAUM: Thank you very much, Jody.

The next item in our agenda is a bittersweet one for some of us, and that is the plaque presentation of retiring VRBPAC members, and for this purpose we call on Dr. Kathryn Zoon.

Dr. Zoon, good morning.

DR. ZOON: Good morning. It's a pleasure to be here this morning, and I think like Dr. Daum, it's a bittersweet meeting for me as well because it's my last VRBPAC meeting. So I just wanted to say a few words today.

It's a special pleasure for me to be here. Our FDA Advisory Committees are one of our most important vehicles at the FDA to provide us with the expert advice and scientific deliberations that help us ponder very important decisions that affect the public health. It helps us make the processes and our scientific analyses public in a way that we can share this information with you and understand the questions and also the importance of the decisions that will be made both for now and in the future with respect to products and policy for the public.

This particular committee, I have to say, has had just a tremendous amount of responsibility, and it has hung tough when it needed

to. It has provided expert scientific advice on important issues, and I think the membership here should feel proud of its contributions both to public health and for dealing with the health and safety of the vaccine and related products that we have asked for your advice.

I'd like to ask Dr. Karen Midthune to please come up and join me. Karen is the Director of the Office of Vaccines, and it really for many reasons is a time when we all reflect on the contributions of this committee. In some ways it's a little ironic that we wait until you all leave, but I think you are appreciated all through the process, and certainly we officially recognize you at the end of your term.

And I want to say to Bob Daum and Walter Faggett and Barbara Loe Fisher -- and, Barbara, it's good to see you -- and also Diane, who I know couldn't be here, but each and every one of you during your term here has provided insight and a diverse opinion on the application and use of vaccines, and that's important. It's important for the process. It's important for moving these products forward and having them being used in the proper way to protect our children, to protect

adults, and I think we are all terribly thankful at the FDA for everything that this committee and particularly the members here today that are leaving us after serving such a what I would say just chock full of challenges on this committee.

And if I could ask each of the members who are here today to come up, Bob, Walter, and Barbara, I'd like to present you with a plaque and a letter from the Commissioner.

I'll start out, and, Karen, while I'm getting this technically challenging activity, would you please like to say a few words?

DR. MIDTHUNE: Sure. I'd just like to echo what Kathy said. We really, really do appreciate your input, and we recognize what a phenomenal time commitment it is to really read through these materials, meeting after meeting, and really come and be so prepared as you are to give us the very important advice. So I would just like to add my thanks because we're asking a lot of you, and we really appreciate it.

DR. ZOON: Thank you. Thank you, Karen.

So I'll start out with Bob Daum, and I'd like to read the letter from Linda Skladany. It says:

"I would like to express my deepest appreciation for your efforts and guidance during your term as a member of the Vaccines and Related Biologics Products Advisory Committee. The success of this committee's work reinforces our conviction that responsible regulation of consumer products depends greatly on the participation and advice of the entire health community.

"In recognition of your distinguished service to the FDA, I am pleased to present you with this enclosed certificate. Thank you."

Bob, congratulations, and thank you for being the Chair.

(Applause.)

DR. ZOON: Bob, I think we're supposed to get a picture.

I think this letter says the same. So I'm not going to read it again, but I just want to thank you so much for your participation. It has really been wonderful.

(Applause.)

DR. ZOON: With that, Robert, I turn the duties back over to you as Chair, and thank you for everything.

CHAIRMAN DAUM: I'd actually like to

take two or three minutes and just make a couple of comments on a soap box as I won't have an opportunity to do this again any time soon.

Being chair of this committee is perhaps the most honored distinction of my entire professional career, and I thank everybody who has allowed me to help in this regard. It has been a way of giving back to the community from which I've taken many things during my professional career.

I'd like to say a special thanks to the people who make these meetings possible. I had the great pleasure of seeing Nancy Cherry this morning, who is the previous Executive Secretary to this committee. Nancy taught me almost everything I know and I think is the owner of the little bell that it has been my custom to ring when we have the committee called to order.

Jody Sachs has stepped into tall shoes, but has done very admirably, and I have every expectation that she will continue to provide excellent support to Dr. Stephens, the new Chairman of the committee who I'm told it's okay to say that.

Bill Freas has also been wonderful help, as has Denise Royster and her staff, making things work.

We've had meetings at an unnamed Hotel H and an unnamed Hotel M, which you currently sit in. I'm very grateful that we have our last meeting in Hotel M, as it offers many, many, many amenities that are much nicer than they often are in Hotel H.

Dr. Stephens, as the incoming Chair, you'll notice is in the hot seat today where he will comment first at the appropriate time. I can tell you, David, that you trade one disease for another. When you come up here the tension is a little bit less in terms of being the first speaker, but there are other issues that will bear upon you, you'll see.

To the previous Chairs, Harry Greenberg, who is here today, Harry taught me to never make the committee do a working lunch. We've got to get up. We've got to stretch our feet. We've got to go to the bathroom. Thank you, Harry, for that lesson.

(Laughter.)

CHAIRMAN DAUM: Pat Ferrieri taught me where eateries were near Hotel H that would provide relief from the cuisine offered therein.

(Laughter.)

CHAIRMAN DAUM: The FDA folks need to be respected. In my view they're heroes quite

literally. It may sound corny to say. The doings of the agency often go on behind the scenes. The culture is an unusual one in that one can't often talk freely in public about things one would like to say.

But I just point to the track record that we Americans are used to in terms of having safe and effective products on the market routinely with almost never, almost never a variance, and it is from their hard work and their determined effort that this is possible.

I take my hat off to all of them. I feel sad that I won't be working with them on a day-to-day basis after this, but I just want them to know that they are in my admiration and esteem and will be forever.

The research that they do is not well known among many sectors of the public. It's extremely important. One of the things I've tried to do under my leadership of this committee is to make people more aware of the research that goes on in the agencies and the crucial importance of it in properly regulating and insuring safe and effective drugs and vaccines.

Our effort was cut short by September

11th. The good news is that a great deal of research funding poured into the agency after that and, of course, partially alleviated the problem.

But there's much more work to do, and, David, I hope that you will continue this effort to provide proper research funding for the agency so that this is not a concern they have to dance to every day.

The Vaccine Shortages Committee provided an opportunity to get some recognition for research effort at the agency in writing, and I was very pleased to help craft a paragraph in that document that called attention to this effort.

Finally, a couple of comments about vaccine safety and public trust. The public, of course, expects the safest vaccine supply possible. They also expect, in my opinion, protection from vaccine associated diseases, and we can't compromise either of these objectives.

There are many people who enter into a dialogue about vaccines, and all of them need to understand in my opinion three rules.

One, the vaccines currently in use for routine childhood diseases are extremely safe, but not always. The vaccines in routine use for

childhood disease are extremely effective, but not always. And the risks of today's vaccine are massively outweighed by the benefits of today's vaccines.

And so I would like to close with a plea to all individuals in this room and beyond who are involved in the dialogue and interaction and discourse about vaccines, from manufacturers to regulators, to public health officials, to academics, to vaccine safety activists. Please continue this dialogue. Please come onto the playing field ready to interact and play the game, but please remember these three rules, the rule about safety but not always, the rule about effectiveness but not always, and the rule about which side of the scale the risk and benefits equation comes down on.

Look at the progress we've made in eradicating or nearly eradicating so many childhood diseases.

For everybody's time and effort and putting up with me and my vagrancies and during this chairmanship, I'm very grateful, and thank you very much.

(Applause.)

CHAIRMAN DAUM: And now back to everyday committee business. I'd like to begin by asking the committee members and temporary voting members and others seated at the table to identify themselves, and, David Stephens, we will begin with you.

DR. STEPHENS: Happy holidays. I'm David Stephens from Emory in Atlanta, and I want to thank Bob for his leadership of this committee.

DR. KATZ: I'm Sam Katz from Duke University, and since you gave me the microphone, I'd like as a non-government employee to make a comments. If I understood correctly, Kathy Zoon said this was her last meeting, and I think it's inappropriate that we don't have some sort of accolade, a plaque, a bouquet of flowers, and other ways of saying that she has been an incredible leader.

If what I read in Science magazine a week or two ago is correct, I think she has been the victim of what is very wrong direction by some of the people directing our government. I know that as members under the conflicts of interest we can't lobby; we can't do this or that, but we need to do something to preserve CBER and see that it has people like Kathy Zoon leading.

Thank you.

(Applause.)

CHAIRMAN DAUM: Thank you, Dr. Katz.

Many of us just learned about this a few moments before the meeting began, but your comments are perfectly appropriate, and I appreciate them.

DR. EDWARDS: Sam is always a hard act to follow.

(Laughter.)

DR. EDWARDS: I'm just Kathy Edwards from Vanderbilt.

DR. SNIDER: I'm Dixie Snider. I'm the Associate Director for Science at CDC. Also I suppose of relevance is that I am the Chair of the Advisory Committee on Immunization Practices at CDC and have other engagements with vaccine issues, such as smallpox, and the Technology Transfer Office at CDC comes under my purview.

And like Sam, I would like to take an opportunity just to make a couple of personal comments. One is to Bob and thank him for his excellent leadership of this committee and to all of the people who serve on this committee.

When I was a member of the committee and over, I guess, the seven years or so I've been

either a member or a consultant, it's been a wonderful opportunity, and I particularly appreciate all of the relationships I have with the people at FDA. I think CDC and FDA have great relationships around vaccines.

I'm really going to miss Kathy Zoon. She's not only a great public servant, but a personal friend, and I think it's a great loss to FDA.

DR. HAMILTON: Holli Hamilton, NIH.

DR. EICKHOFF: Ted Eickhoff, University of Colorado.

I would like only to say that, Bob, the meetings that I have been privileged to attend have vastly benefitted by your guidance as Chair. So thank you very much.

And to Kathy, again, best wishes.

DR. COX: Nancy Cox from CDC.

DR. GELLIN: I'm Bruce Gellin. As of six weeks ago, I'm the director of the National Vaccine Program Office at HHS.

DR. STEINHOFF: I'm Mark Steinhoff from Johns Hopkins University School of Medicine and School of Public Health.

DR. MYERS: I'm Martin Myers from the

University of Texas at Galveston.

DR. OVERTURF: I'm Gary Overturf. I'm Professor of Pediatrics and Pathology at the University of New Mexico.

DR. DIAZ: I'm Pam Diaz, the Director of Infectious Diseases for the Chicago Department of Public Health.

DR. FAGGETT: I'm Walt Faggett, pediatrician here in D.C., Medical Director for Medicaid in D.C., and I, too, want to express my appreciation of Bob Daum's leadership for this past four years. It has really been a pleasure serving on the committee, and the experience here is really going to help us, I know, in D.C. as we look forward to the challenge of smallpox immunization. Some of the decisions that we make will really benefit from the exposure I've had here on this committee.

So, again, I'm very privileged to have served and will look forward to staying in touch.

Thank you.

DR. MARKOVITZ: I'm David Markovitz from University of Michigan.

DR. PARSONNET: Julie Parsonnet from Infectious Diseases at Stanford University.

DR. FISHER: Barbara Loe Fisher with the

National Vaccine Information Center.

And I'd just like to say it has been a great privilege to serve on this committee. I believe that we need a strong FDA, and I particularly want to thank Kathryn Zoon for making this possible for me to be on this committee.

DR. DECKER: Michael Decker, Aventis Pasteur and Vanderbilt University, Department of Preventive Medicine.

Bob, you've done a great job chairing, and I particularly have admired the way you've insured full and fair discussion

DR. GOLDBERG: Judith Goldberg, Director of Biostatistics at New York University School of Medicine.

Bob, you've been a great Chair. I've learned a lot watching you.

And, Kathy, you've led this group to allow free and open dialogues, and you've been absolutely responsive to every request that this committee has made, and I've seen the changes in documentation as a result of all of that. Thank you and best of luck.

DR. PRATT: Douglas Pratt, FDA.

DR. MINK: ChrisAnna Mink, FDA.

CHAIRMAN DAUM: While Dr. Sachs is getting ready, I'm Robert Daum. I'm Professor of Pediatrics at the University of Chicago.

DR. SACHS: And I'm Dr. Jody Sachs. I'm the Exec. Sec. of VRBPAC. Welcome.

CHAIRMAN DAUM: Thank you very much, committee members and temporary voting members and FDA colleagues.

We'll now turn to some noncontroversial matters for the rest of the morning, and that is consideration of FluMist influenza virus vaccine, and we'll begin with Dr. Mink, who will begin with an overview of FluMist issues.

Dr. Mink.

DR. MINK: Good morning. I'm ChrisAnna Mink from CBER. I'd like to welcome you to today's VRBPAC.

I'll begin with an overview of the product which is FluMist. FluMist influenza virus vaccine, trivalent A and B contains three strains of live attenuated, cold adapted, temperature sensitive influenza viruses; two Type A, H1N1 and H3N2, and one Type B. Each .05 mL dose contains ten to the seventh TCID50s of the three strains in normal allantoic fluid, which will be abbreviated NAF

throughout my presentation.

A review of the regulatory time course is shown on this slide. The original BLA was submitted to CBER on October 30th of 2000. Our first VRBPAC meeting was July 26th and 27th of 2001, after which CBER issued a complete response letter, a CRL, on August 31st, 2001, and we received the sponsor's response to our first letter on January 7th, 2002.

Our second letter was issued to the sponsor on July 10th of 2002, and we received their response on August 26th, 2002.

On November 1st, 2002, the sponsor revised the age indication, which I'll discuss briefly, and that brings us to today's meeting.

Some changes have been requested by the sponsor on the indication side. Originally the proposed indication for the age was from 12 months to 64 years, and as I mentioned, this has now been revised to 60 months through 64 years.

Originally a request for an indication for travelers to areas where influenza viruses were circulating was included and this has been removed. Also in our history we have some unresolved concerns from VRBPAC 2001, and we are now returning to the

committee.

To briefly review 2001 VRBPAC, the efficacy vote was divided for children/adolescents and for adults. For the one to 17 years of age group, the committee at that time voted eight yeses and seven noes, with five of the seven members who were voting noes stated they would have likely voted yes if they were requesting an age starting in older children, for example, 15 to 24 months of age.

The expressed concerns for children and adolescents included that there were few subjects under two years of age included in the database. We had no concurrent immunization data. There was no H1N1 field efficacy, and some committees expressed concern that we are extrapolating data for children from seven to 17 years of age.

The efficacy for the adults included 13 yes votes and two no votes for the age group of 18 to 64 years of age. Expressed concerns included that there were few subjects over the age of 50.

There were some concerns about defining a healthy population for receipt of this vaccine. No re-vaccination data was provided at that time. No concurrent immunization data were available, and there were some concerns expressed about the use of

clinical endpoints, i.e., effectiveness, not confirmed with influenza cultures' efficacy data.

The safety vote was across the entire age cohort of one to 64 years of age. At that time there were five yes votes and nine no votes; subsequently, on the last day revised by the committee chair, as four yes and ten no votes.

The express concerns at that time included that the final data for some of the critical studies had not yet been submitted to CBER; the possible association of FluMist with adverse respiratory events, including pneumonia and asthma and wheezing.

Other concerns included the occurrence of other adverse events, AEs, occurring post vaccination. There were few subjects under two and over 50 for the safety database. Again, no concomitant immunization, and there was a paucity of transmissibility data.

There was also a discussion about the possibility of reassortment, including with wild type influenza, and the risk of reversion of these attenuate strains.

The current indication being sought and to be discussed today is FluMist is for the active

immunization for the prevention of disease caused by Influenza A and B viruses in healthy children adolescents and adults from five years, greater and equal to 60 months, to 64 years of age. A two dose regimen, 60, plus or minus 14 days, for the first use of children five to eight years of age is being requested and one dose for all others and for those over nine years through 64 years of age.

With consideration for the revised age indication and the availability of the final effectiveness and efficacy data, as well as additional safety analysis of FluMist will all be presented today for the committee's deliberation. To help frame the day, I will present the questions.

Question one will be safety for vote. Are the data adequate to support safety of FluMist for individuals five to 17 years of age, 18 to 49 years of age, 50 to 64 years of age? Please consider data related to the respiratory events, such as asthma and upper respiratory infections, shedding and transmission of vaccine strains following receipt of FluMist, and annual revaccination.

If the data are not adequate for specific age groups or there are other safety

concerns, please discuss what additional data should be requested.

Question number two is efficacy, also for a vote. Are the data adequate to support efficacy in FluMist in individuals five to 17 years of age, 18 to 49 years of age, and 50 to 64 years of age?

If the data are not adequate for specific age groups, please discuss what additional data should be requested.

Question three is a discussion point. Clinical studies for release of new strains: please comment on the design and endpoints for the clinical study performed in adults which will be presented today for the release of new strains.

And discussion point number four: if the data are adequate to support safety and efficacy, please discuss what additional information, if any, should be requested from post marketing studies.

With this orientation, I turn the meeting back to Dr. Daum.

CHAIRMAN DAUM: Questions from the committee for clarification of Dr. Mink's orienting remarks? Dr. Faggett, please.

DR. FAGGETT: Bob, under the efficacy vote, the first slide, it was stated that a vote for efficacy data for supporting indication, one to 17 years of age, five, seven no; the request was starting at older age, 15 to 24 months. I'm not sure that that's really stated correctly.

DR. MINK: That information is from last year's VRBPAC, and some of the members who voted no for the age group of 12 months through 64 years, five of the seven who voted no expressed that they would likely have voted yes if an older age is being requested, such as 15 months or 24 months of age.

DR. FAGGETT: Okay. Thank you.

CHAIRMAN DAUM: That's how I remember it Dr. Faggett. What's your concern?

DR. FAGGETT: I thought it was, well, like three or four. I thought it was over two. I didn't recall it being less than two. So I stand corrected if that's in the minutes.

CHAIRMAN DAUM: I think this is the way it was.

DR. FAGGETT: Okay. Thanks.

CHAIRMAN DAUM: Good. Let's continue then. We're next going to turn to our sponsor, Medimmune Vaccines, and begin with a presentation

from Dr. Young -- this is Dr. Young? Good morning, Dr. Young -- who will give us an overview and a product profile.

DR. YOUNG: Good morning, everyone. Thank you very much.

As Dr. Daum mentioned, I'm Jim Young. I'm actually very excited to be here today. I just hit a very important milestone, and for those of you who know me, think that that probably refers to the fact that I just turned 50 years old yesterday, but it's actually not that. For those of you who are parents can appreciate the fact that I have a three months old son who just slept through the night for the first time last night.

(Laughter.)

DR. YOUNG: And 11 and a half hours. I'm so excited about that. I was beginning to forget what sleeping through the night really felt like.

But actually I'm also very excited to be here today to talk about FluMist, which we believe is an important new product. As I said, I'm Jim Young. I'm President of Research and Development at Medimmune.

We're a biotech company that's located

about ten miles north from here in Gaithersburg, Maryland.

You can see from the first slide here the sponsor has changed for the product since the last time the VRBPAC committee met, when it was Aviron, and the reason for that is that in January of this year, Medimmune merged with Aviron and formed a subsidiary called Medimmune Vaccines that now actually has regulatory responsibility for the product.

What I'd like to first do is echo some comments by Dr. Daum and acknowledge the tremendous amount of work and diligence that the review staff has demonstrated during this review process. It has just been a tremendous amount of information that we've submitted to them in the course of this review, and it's really quite a lot of work to sift through all of that information and go through the review.

I'd also like to thank the committee members for finding time in what I'm sure is a very busy schedule this time of the year to actually have this special meeting to review Synagis -- review FluMist. Excuse me.

(Laughter.)

DR. YOUNG: Oops, wrong product. That's our other product.

To review FluMist and give you an update on FluMist.

CHAIRMAN DAUM: You thought I wasn't listening, didn't you?

(Laughter.)

DR. YOUNG: I'm so used to talking about Synagis.

And give you an update on the product and, in particular, address unresolved questions that were raised at the last committee meeting now that a full data package is available for the product.

As Dr. Daum mentioned, I will first begin the sponsor presentation by providing a very brief overview and product description, and then what I'd like to do is describe for you the new proposed indication that Dr. Mink briefly reviewed for you in her presentation. I'll then turn the presentation over to Dr. Ed Connor who is our Senior Vice President of Clinical Development, and Ed will give you an overview of the clinical data that supports the efficacy and safety for the product. It will also give you information about

transmission and vaccine virus stability, both phenotypic and genetic stability.

You are, of course, all aware of the significant morbidity and mortality associated with influenza as it is the most common cause of medically attended respiratory illness in the United States among all age groups. It's estimated that there are about 70 million lost work days, 38 million lost school days, and an astonishing 20 to 50,000 deaths annually due to influenza in the United States.

Although about 60 to 90 million doses of the inactivated flu vaccine are administered annually to protect against influenza, most of this goes to the high risk individuals. It turns out that it's estimated that about 150 million healthy Americans are currently not vaccinated against influenza; that less than ten percent of healthy children, less than 30 percent of healthy adults actually get their flu shots, and clearly this is a major concern of the ACIP.

As many of you may know, they recently broadened their recommendation for influenza vaccine to include health infants and toddlers and their contacts. It is in this healthy population that we

believe FluMist can fulfill an important public health need.

Given what we believe to be its excellent safety and efficacy profile and ease of administration such that adequate supplies of the inactivated vaccine can be made available for the high risk individuals, as Dr. Mink mentioned, FluMist is a cold adapted, temperature sensitive, live, attenuated influenza virus vaccine that's administered by intranasal mist, hence our very creative name for the product, FluMist.

It is made from vaccine strains that were originally derived by Dr. John Maassab at the University of Michigan back in the mid-'60s wherein he took an Influenza A H2N2 isolate and a Type B clinical isolate, and he independently passaged both of those isolates sequentially in primary chick kidney cells and embryonated hens' eggs at progressively lower and lower and lower temperatures.

And at the end of that process what he derived were some viruses with some very interesting properties. First, they were cold adapted, meaning they would grow in the cooler upper airway.

They were temperature sensitive so that

they would have limited replication in the lower airway.

And they were attenuated. They wouldn't cause disease in a ferret model of human influenza, a property that was later also shown in human volunteers.

Now, what we do is we take these master donor viruses that Dr. Maassab generated, and we introduce into them the genes coding for the hemagglutinin and neuraminidase surface glycoproteins that come from the contemporary strains that are circulating in the population that we want to vaccinate against.

We've actually made 14 different versions of these different versions of these vaccine strains and tested them clinically.

Now, today you may also hear the term "CAIV," cold adapted influenza vaccine. These are vaccines that were derived from the same master donor viruses that Dr. Daum had generated, most of that work being done at the NIH. Nineteen of those strains were developed and tested clinically in about 8,000 human volunteers.

Now, at the last VRBPAC presentation, Dr. Brian Murphy gave a very comprehensive overview

of the important and unique properties of these master donor viruses and of the vaccine strains that are derived from them, and I'm certainly not going to try to replicate his talk. But suffice it to say Brian presented information that there are at least four mutations in each of four genes for the MDV strains that confer attenuation in the ferret model.

We know that there are at least seven mutations in the A strain and eight in the B strain. We also know that these viruses are extremely phenotypically stable. In any laboratory passage study, animal studies, even clinical studies, we've never seen a revertant of these attenuated phenotype.

And, frankly, that's not very surprising because given that there are at least four mutations in the MDV that confer attenuation, at a mutational frequency of ten to the minus five for any animo acid to change, with those four mutations needing to revert back to the wild type sequence, all four of them required to revert back to the original wild type sequence, that would occur at a calculated frequency of ten to the minus 20.

And in fact, if it were all seven or eight mutations that need to revert back to the wild

type sequence to generate a wild type virus, it would be ten to the minus 35 or ten to the minus 40.

Now, to put that in perspective, we know that children shed at most during their peak time of shedding ten to the four of vaccine virus. We know adults actually shed about 100 times less than that. If we assume, however, that everyone sheds ten to the four viruses when they are infected with this vaccine and then we assume that they make 1,000 times more virus in their upper airway, if we were to immunize all 300 million Americans today with this vaccine and they all produced ten to the seven virus not for just the two to nine days that they normally produce it, but forever more, for the rest of their life, it would take 100 years to produce ten to 20 viruses.

Now, this is a schematic representation of the influenza virus structure and the genetic make-up of the virus. You can see it's an envelope virus. It has eight RNA segments contained within the virus. Two of these segments, the HA and the NA, code for the hemagglutinin and neuraminidase surface glycoproteins.

The hemagglutinin is involved in virus cell entry; the neuraminidase involved in budding of

the virus from the infected cell, and both of these proteins are the main targets of protective immunity.

The other six gene segments code for a number of different virus proteins that are involved in virus replication and immune evasion.

Now, when we want to make a new vaccine strain, what do we do? We start off with those Dr. Maassab's master donor viruses, and we co-infect cells with the master donor virus chick embryo kidney cells. We co-infect cells with the master donor virus and the new wild type strain that is circulating that we wish to make a vaccine against.

Now, when these viruses go into the same cell, they begin to replicate their RNAs, and they actually end up shuffling them, and the progeny virus that comes out of those cells has various combinations of these different genes from the two viruses, and there are actually 256 different combinations that are possible.

What we do is we then go and fish out a virus that is what we call a 6:2 vaccine strain that derives two genes, the hemagglutinin and neuraminidase genes from the wild type virus because we want to make immune responses to those two

proteins, and the other six genes come from the master donor virus which confer the attenuated properties of this master donor virus on this new vaccine strain.

Now, once we've derived that 6:2 vaccine strain, what we then do is propagate it or manufacture it in specific pathogen free eggs. Now, these eggs come from chickens that have been extensively tested to demonstrate the absence of any adventitious agents in those blocks.

We also have an extensive testing program of the vaccine intermediates, the bulk vaccine virus, and the final product.

And as Dr. Mink mentioned, we also do a safety testing of the new vaccine in 300 adult volunteers to insure that it is of the right attenuated phenotype.

As she also mentioned, the vaccine is comprised of a trivalent blend of ten to the seven infectious particles of each of the three currently circulating influenza virus strains that are also recommended for the inactivated vaccine, and it's contained in half an mL dose. This product is presented as a unit dose, which is stored frozen with no thimerosal in this little sprayer device.

And the way this works is you basically take this sprayer and thaw it in the palm of your hand. You then remove the cap off the sprayer, insert the end of the sprayer up into the nostril and depress the plunger, and that delivers half the dose to one side of the nose.

You then take off this little dose divider clip, insert it into the other side of the nose and press the plunger and complete the administration of the dose.

Now, the sprayer actually generates a large particle mist that is deposited in the upper airway where the virus will replicate. As Dr. Mink also mentioned, there is a single annual dose recommended for individuals that are nine years or older, and it is recommended that a child that is less than nine years old receive two doses spread 60 days apart if it's their first time for receiving an influenza virus vaccine.

Now, at the last VRBPAC meeting in July of 2001, it was felt that the data were adequate to establish efficacy in healthy individuals, and as was pointed out -- I think this was right -- the vote that was actually for children one to 17 years was eight to seven in favor of having shown efficacy

and in adults 18 to 64, 13 to two.

However, it was noted that the sample size at the lower end of the proposed age spectrum in individuals 12 to 24 months was less robust, and that had the indication for children been two to 17 years, the vote would have been 13 to two, and that was reviewed by the Chairman, Dr. Daum.

When the question of safety was asked in the total population requested, age one to 64, the votes was four to ten with six of the votes qualified as provisional, and that was mainly because the final safety data had not yet been submitted to the agency and, consequently, the CBER review was still ongoing.

It was also noted that there were additional analyses that needed to be completed to resolve some safety questions and particularly the ones with respect to pneumonia and asthma. It was also noted that concurrent immunization data were not available and was needed for children under 24 months of age.

Now, what progress have we made since the last VRBPAC meeting? Well, first of all, we've responded to two complete response letters from CBER, and in so doing established the 20 studies

which would serve as the final data set for consideration in the BLA. Fourteen of these were placebo controlled trials and six were open label trials.

In total, the data from these studies represented a total of 20,000 subjects receiving approximately 28,000 doses of FluMist.

We also submitted final study reports for the two very large safety studies involving about 15,000 individuals, 15,000 children, AV019 and AV012, and also the final study report was submitted for a Finnish day care study that provided some information on transmission and virus shedding.

And when the final analyses were conducted on all of this data, it showed quite clearly that there was no signal for pneumonia and that there was a possible signal for asthma or wheezing exacerbation in children less than 60 months of age.

At the last VRBPAC meeting we also indicated that a concurrent immunization study had just been started with FluMist and MMR and VARIVAX, and we've actually recently completed full enrollment in that study and we're now in the final follow-up period with those children.

So for consideration today at today's meeting, here is the proposed indication. For active immunization to prevent Influenza A and B in healthy individual, healthy children and health adults ages five years through 64 years of age.

We are not proposing FluMist be used in individuals with a history of underlying medical conditions which predispose them to bad outcomes with wild type flu, and those are listed here on the slide.

We're also not proposing that the product be used concurrently with any other vaccine, frankly, until we have the data that would support that use.

So with that I will conclude my introductory comments and now turn the presentation over to Dr. Ed Connor, who is going to give you a review of the clinical data supporting the efficacy and safety of the product.

Ed.

CHAIRMAN DAUM: I think maybe before we call on Dr. Connor we might see if there are some clarifying questions from the committee. We'd like to keep questions and comments at this point to issues that require clarification of what you said,

and then we'll have opportunity for a more general discussion of sponsor related issues after Dr. Connor is complete.

Dr. Snider, please.

DR. SNIDER: Thank you.

Two relates questions. I appreciate your reminding us about the particle size and 98 percent being larger than ten microns. I presume the other two percent has the potential for reaching the lower respiratory tract, although not all of it will.

The question is: do we know any more than we did in 2001 about the distribution?

And then very much related to that, you spoke about, and I guess we'll be talking more about, shedding. I know that nasal swabs and one would anticipate that most of the shedding would be from the nose where most of the virus is deposited. But is there any information about the virus present in the lower respiratory tract?

DR. YOUNG: I think about all we can say about that is based on the scintigraphy studies that we've done where we've labeled material and then deposited it into the nose, and we've done radiation surveys of various components of the abdomen and

have shown that the vast majority of it, as you mentioned, ends up in the upper airway.

And when we do field screens of the lungs, we see what we think is just background radiation coming from the esophagus where some of the vaccine actually hits the back of the mouth and is swallowed into the stomach. We see some radiation in the esophagus that over time quickly moves down into the stomach.

And what we've seen in the scintigraphy studies is that if you use nasal drops, you see the same amount of radiation in the lungs. So I don't think that we believe that there is very much of this that actually gets down into the lung, and in fact, even if there is a small amount, given its temperature sensitive phenotype, we would expect very little replication in the lung itself.

CHAIRMAN DAUM: Ms. Fisher.

MS. FISHER: You made a statement that children shed vaccine virus more than adults. Do you know why?

DR. YOUNG: Probably because of the lack of any preexisting immunity. Adults, of course, will have had numerous encounters with flu virus over the course of their lifetime, and there is some

low level immunity that's going to be protective against the virus that would suppress replication of the virus in adults.

I think it turns out that probably young cells are probably a more fertile environment for the growth. We tend to see better replication in younger cells, not that we have old cells, but I think it's a combination mainly driven by the lack of immunity in children where they can shed more virus for a longer period of time.

Adults shed for only about two days. Children will shed for on average about nine days, and as I said, about 100 times more virus than adults.

MS. FISHER: Well, then if everyone uses the -- the children use this vaccine, then they'll grow up to be adults that will continue to shed more virus, right?

DR. YOUNG: No, actually they will get immunity to the virus obviously.

MS. FISHER: they will?

DR. YOUNG: And then, of course, they will shed less virus as well.

MS. FISHER: As long as they keep getting vaccinated.

DR. YOUNG: No, actually, well, they'll need to get vaccinated against the new contemporary strains that are circulating because it changes those two surface glycoprotein and you'd need to reeducate or educate the immune system to those new surface glycoproteins.

But once you've encountered flu, you know, the risk is lower because you have some cross-protective immunity, but you need to get better immunity against the contemporary strains that are changing in the population.

MS. FISHER: Thank you.

CHAIRMAN DAUM: Dr. Markovitz, please.

DR. MARKOVITZ: Yes. What can you tell me about how you pick out the proper reassortment virus? You know, you're looking for the 6:2 mix. How do you know that you have the right six genes and the right two genes?

DR. YOUNG: Yeah. We actually have a pheno-genotyping assay that we use. It's a RFLP type assay where we can actually -- what we first do is once we have the mixture of viruses, they get passaged in eggs in the presence of antibody to the master donor virus to suppress replication of any residual master donor virus, and so what we get out

are mainly viruses that have the hemagglutinin and the neuraminidase from the new wild type strain.

We then clone those viruses out, dilute them out and get individual clones from the progeny from that co-infection, and then we genotype each of those clones, and we have a specific assay where we PCR the gene segments and cut them with restriction enzymes that are specific for either the master donor virus version of the gene or the wild type version of the gene.

What we actually do as a prerequisite to that is we sequence the entire genome of the new wild type strain that we're going to make a vaccine for so that we know what restriction enzymes to use and what primers to use to pull out the wild type gene specifically.

CHAIRMAN DAUM: Very good.

DR. YOUNG: Anything else?

CHAIRMAN DAUM: Dr. Stephens, we're looking for comments here to clarify issues raised by Dr. Young. We'll have an opportunity after Dr. Connor speaks to explore some of these issues that committee members are raising in detail per your pleasure.

Dr. Stephens.

DR. STEPHENS: This is a clarification regarding the reversion rate, which you suggest is low, less than minute ten to the minus 20.

What about reassortment, which is more of a concern with wild type and where I think the frequencies would be considerably higher?

DR. YOUNG: Yeah, with respect to reassortment, there's really two different situations you need to consider when you think about reassortment. The first is during an interpandemic period where we're just immunizing against strains that are already circulating in the population. There's actually lots of reassortment going on between the A strains that are circulating now. They've seen H1N2s. So that happens. We know that happens, and that can happen if and only if an immunized individual also has a wild type flu infection at the same time.

And you're right. If that happens, you can get a reassortment between FluMist and that wild type strain. But you need to remember the FluMist comes from a human strain that's already been in the circulation; that we have reassortment that has occurred between strains that are already circulating, and at worst, what you can get back out

is a wild type strain because the cold adapted genes that are in the attenuated virus can only make the wild type attenuated.

So at worst if you didn't attenuate the wild type, you'd get back out wild type, and that's going on all the time anyway. You've got that circulating all the time anyway, and so you would have already put that wild type into the person anyway.

So in terms of normal epidemic vaccination against normal epidemic strains, the risk of generating a super virulent strain is virtually impossible because the genes that we have in the FluMist virus are attenuating, and we know that from data that Dr. Murphy presented last time. When you just put individual genes and have done the experiments where they put individual genes from these master donor viruses into wild type strains, you generally get a strain with lower virulence and not higher virulence.

Brian, I don't know if you want to make a comment about that. You've certainly done more of this type of work than anyone else in the world.

DR. MURPHY: Although I don't have the exact data, we probably have made between ten and 15

different mixed gene constellation viruses from the master donor A virus, and none of those showed a virulence that was greater than wild type. Almost every one of them had an attenuated phenotype.

DR. YOUNG: Thanks, Brian.

Now, the other setting where you worry about reassortment is if we wanted to use FluMist as a vaccine for a new pandemic stream before the virus was actually in our population, and clearly you wouldn't want to do that because now you could get reassortment between the new pandemic FluMist with the H1N1 or the H3N2 viruses that are circulating now and prematurely introduce the pandemic virus into the population.

So clearly, you would want to want to wait until the public health authorities deemed it appropriate to now start immunizing with a FluMist pandemic strain because you felt that the risk of spread of the pandemic virus was so significant that you wanted to try to immunize people as quickly as possible and the virus was already in the population anyway.

Okay? You don't look satisfied.

DR. STEPHENS: Well, I think the point was the issue in recombination. I mean the issue is

reassortment and recombination. It's probably not reversion. I think you've pretty well demonstrated that that's very, very low, but I think there are issues with reassortment that we need to talk about further.

CHAIRMAN DAUM: Dr. Decker.

DR. DECKER: I've got several questions that follow up on Dr. Stephens' questions. The vaccine virus differs from circulating wild virus in two ways. It's cold adapted and it's attenuated. Are those --

DR. YOUNG: And it's temperature sensitive.

DR. DECKER: Okay. thank you.

Do those three characteristics reside in different or in the same genetic changes? In other words, is one set of changes simultaneously making it cold adapted, temperature sensitive and attenuated? Is it in two of those three and the third is based elsewhere, or are all three genetically distinct?

DR. YOUNG: The answer to that question is that they probably are overlapping. I don't think that given the three different phenotypes that they are al in the same mutations. We know actually

that there are five mutations for temperature sensitivity in the A strain, four mutations in the B strain.

We have now generated viruses that have all of the single point mutations distributed singly in viruses and are testing those for attenuation and cold adaptation. So hopefully in the not too distant future we will have sorted that out, but my guess is that there's probably some overlap that the temperature sensitivity is also related to the attenuation.

DR. DECKER: All right. Your response to Dr. Stephens focused on the fact that a reassortment with the circulating strains would just present the same neuraminidase and hemagglutinin antigens that everybody is seeing anyway, which is fine. That's reasonably straightforward.

But the question that I was hearing that I didn't hear an answer to is would it be possible for a reassortment or similar genetic combinations to, for example, produce a virus that is cold adapted, no longer temperature sensitive, and no longer attenuated and which, therefore, could exploit the human ecologic niche more effectively an the current virus and create something that would

pose a new medical issue.

DR. YOUNG: No actually what you would then get is the wild type virus back. That's already --

DR. DECKER: No, the wild type virus isn't called adapted. So you'd produce a virus that could replicate both in the nose an din the lung.

DR. YOUNG: Actually a lot of the wild type viruses are cold adapted, and actually a number of them are also temperature sensitive.

But I think the point is that most of the mutations -- there are four different genes for attenuation. So automatically if those four genes, any one of them, ended up in the wild type virus, it would attenuate the virus, period. It would just attenuate it.

The other two, we're not sure yet if any of the mutations in those are related to cold adaptation or temperature sensitivity, but it would be certainly no worse to get one of those gene than if a reassortment occurred between the genes for an H1N1 virus and the internal genes for an H3N2 virus.

CHAIRMAN DAUM: Thank you.

I'd like to move on now to Dr. Young's presentation, and then we can have a general

discussion where committee members can explore these issues further should they wish.

I would like to call on Dr. Connor, who is the next Medimmune speaker, and hearing cell phones and beepers going off in the room, I would like to ask once again that everyone in this room be respectful of the committee deliberation and either turn them off or turn them to vibrate mode.

I thank you for your cooperation.

Dr. Connor.

DR. CONNOR: Thank you, Dr. Daum, and good morning.

First of all, this committee has heard in some considerable detail the data about the safety and effectiveness and efficacy of FluMist at the prior VRBPAC presentation. You heard from the principal investigators of each of the pivotal studies, Dr. Bob Belshe, Dr. Steve Black, and Dr. Kristin Nichol, the data on adults and children, safety and efficacy. And those individuals, as well as representative folks from the former sponsor presentation at the last VRBPAC, are here with us today. Steve actually couldn't make it today because he was ill, but the other folks are here, as well as Tony Piedra and Manju Gaglani, from Baylor

who conducted the ABO 12 study, the large safety trial of FluMist in the field.

That body of data is also supported by what is literally decades of research on the predecessors of FluMist, the monovalent and divalent cold adapted vaccines.

My purpose this morning is really to do three things. First of all, what I'd like to do is to review the efficacy-effectiveness data briefly with you, as well as the safety of FluMist in children and adults, and to provide the final data set with regard to the specific open safety questions that were included in the last meeting. Those specifically include asthma and wheezing and pneumonia.

And lastly, I'll provide to you some data on the vaccine virus shedding and transmission issue.

The principal studies that were conducted to support the efficacy-effectiveness of FluMist in children include the pivotal trial, which was AV006, the study conducted by Dr. Belshe, and was a field trial, a two year field trial, demonstrating efficacy for H3N2 and for Type B.

In addition to that, because H1N1 was

simply not circulating during the years in which AV006 was conducted, a challenge study was done with H1N1 using the vaccine strain and demonstrated efficacy of 83 percent.

In adults, the initial trial of efficacy were done by John Traynor, and that study, 003, was a wild type challenge study demonstrating efficacy of 85 percent.

AV009 was the pivotal field trial demonstrating effectiveness of FluMist in adults, and those studies conducted by Kristin Nichol looked at effectiveness measures, that is, disease and illness measures as primary outcomes.

I'm going to focus my review time on the pivotal efficacy trials.

AV006 was the pivotal efficacy trial in children, as I mentioned, conducted by Bob Belshe. It was a randomized, double blind, placebo controlled trial of 1,602 healthy children between the ages of 15 and 71 months of age at entry.

These children received either one or two doses of FluMist in year one, and an annual revaccination dose in year two as a single dose.

There was active surveillance for illness and illness cultures, and the primary

endpoint of the trial was culture proven influenza.

During the time that the trial was conducted in year one there was an A/Wuhan H3N2 and a B virus that were well matched to the vaccine, and during the second year an A/Sydney H3N2 circulated, which was mismatched.

The primary efficacy results are shown on this slide and clearly demonstrate that FluMist efficacy of approximately 93 percent against culture confirmed influenza, and what you can see here is 92.6 percent efficacy in year one and comparable efficacy for other outcomes that were measured in the trial.

As I mentioned, in addition, this study gave us the opportunity of looking at annual revaccination, and here in year two when there was a mismatched strain circulating, one can see efficacy point estimates of 87 percent comparable to in year one; in addition, comparable efficacy in the other outcomes that were measured.

One of the things that's important to note about these studies also was that there were very tight confidence intervals around the point estimates of the effect in both of the years.

In addition, we then looked at the AV006

trial to garner data regarding the efficacy of children in the various age groups of patients that were studied, and here what you can see is the efficacy by age group through each of these various age cuts.

And first of all, the point estimates of the efficacy are quite good compared to the population as a whole. The confidence intervals are quite tight, even within these age subgroups, and for children above 60 months of age, there was point estimates of efficacy of 90.6 in year one and 86.9 in year two.

It was also true that children who entered the second year of the trial actually had aged to 83 months by the time that they entered, and I have provided those estimates of efficacy here also.

You can see, again, that the confidence intervals are quite tight around the point estimates of efficacy, and there's no trend toward any changes in the efficacy, and there's no trend toward any changes in the efficacy according to the age group of the patients that were studied.

The primary trial, the field trial for adults was AV009, as I mentioned. This was a trial

that was randomized, double blind, and placebo controlled. It enrolled 4,561 healthy working adults. That included ages 18 to 64 years.

Patients received a single dose of vaccine, and the primary endpoint for these trials was effectiveness measures. The primary endpoint was actually any febrile illness, and there were a number of secondary measures of effectiveness, that is, disease/illness outcomes in contrast to culture proven outcomes.

The secondary endpoints are listed here, and there were a number of other illness definitions that were also measured: febrile URI, severe febrile illness, which were pre-specified, as well as post hoc analyses that were conducted with the CDC definitions for influenza like illness and the Department of Defense definitions.

During this year of AV009, the circulating strain was A/Sydney, which was an H3N2 and was mismatched to the vaccine strain.

This is a list of the various illness definitions that were used during the conduct of the trial, and as Dr. Nichol mentioned in her presentation to the VRBPAC last year, one can see that any febrile illness, while it's actually a

fairly sensitive measure of detecting disease, it's not a very specific measure for influenza.

And each of these other definitions which include various combinations of more fever or consecutive days of symptoms are actually much more representative of influenza like illness, and so that distinction is listed here. You can see each one of the combinations for each illness that were specified.

Now, these are the primary outcome results for the AV009 trial, and what you see here are a percent reduction, FluMist compared to the placebo group, for each of the illness definitions, and here what we're showing is occurrence of those illnesses.

And while there was not a statistically significant difference in the groups for any febrile illness, there were statistically significant in all of the other outcomes that were more specific for influenza.

These activity levels, that is, a 25 percent or so reduction in effectiveness measures are actually very impressive because remember that effectiveness is measuring the total disease burden, and influenza represents some portion of that.

So in order to be able to effect effectiveness changes one needs to have very high levels of vaccine efficacy. These actually have been studied for TIV in which CDC investigators have demonstrated that effectiveness measures or reductions of about 34 percent are associated with vaccine efficacy, that is, culture confirmed efficacy, of approximately 89 percent, and Bob Belshe showed previously in the AV006 data that in children effectiveness measures of a reduction of approximately 20 percent were associated with culture confirmed influenza reductions of approximately 95 percent.

So these are very highly impressive results in terms of measures of effectiveness.

These data are the percent reduction for the other measures that were looked at in the study: days of illness, days of missed work, health care provider visits, and days of antibiotic use, and you see here the same percent reduction with the various illness definitions shown at the bottom of the slide.

What you can see here are significant reductions in all of these parameters for virtually all of the disease designations and even for any

febrile illness the less sensitive or less specific diagnosis, there were significant reductions in days of illness and days of antibiotic use.

Now, in addition, one of the issues that we've been asked to address through interactions over the last months has been the question of the 50 to 64 year old population within the AV009 study.

And what we show here, first of all, obviously in doing this we're looking at subset analyses in a study in which the study was obviously not designed or powered to look at those subsets. But importantly, if one takes the 50 to 64 year old population, which is shown here in blue, compared to the total adult population in the AV009 study, what we're looking here for is evidence that the 50 to 64 year old population is somehow different than the population as a whole.

And what you can see is, while in occurrence we didn't see differences in the 50 to 64 year old population, for each of the illness definitions actually even including occurrence, when the DOD-ILI designation was used, we saw differences in each of the groups comparable at least to the population as a whole.

And the other aspect of this analysis is

that when you look at disease severity measures, particularly days of missed work and health care provider visits, there are highly statistically different differences observed both in the 50 to 64 year old population as well as in the population as a whole.

So the general trend and pattern within that age group is consistent with us not seeing evidence that that population was substantially different than the population as a whole, the randomized population.

That's actually illustrated here again with data that Kristin Nichol provided, which shows the analyses for febrile URI, one of the more specific influenza diagnoses, and here what is shown is the point estimates and the confidence intervals for the all patient population, 50 to 64 year olds, and 18 to 49 year olds.

And what you see, first of all, is for this illness as a nation, and there are others that are very comparable to this, for each of the measures of effectiveness you see that, first of all, the point estimates of each of these are very tight. They're very close to each other, but the confidence intervals are essentially all

overlapping, and when they weren't overlapping or when the point estimate was outside of the confidence interval, it was actually higher for health care visits for the 50 to 64 year old.

So I think in looking at that kind of assessment, one can glean evidence to suggest that or, rather, we don't have evidence to suggest that there was any significant difference between the 50 to 64 year old population and the population as a whole.

So from an efficacy-effectiveness perspective, we believe that we've demonstrated that FluMist was highly effective in the prevention of influenza in both healthy adults and in healthy children.

We've also demonstrated that efficacy and effectiveness was observed across all of the age subgroups that were studied in these trials. Efficacy in children greater than 60 months was similar to the population as a whole and to the younger children on AV006.

We've also demonstrated that effectiveness in 50 to 64 year olds was similar to the effectiveness in the randomized group, albeit that population was a smaller group. The confidence

intervals were somewhat greater. They, by and large, represent in that study about ten to 11 percent of the population as a whole.

And lastly, field efficacy was established for H3N2 and for B strains. H1N1 just didn't circulate during the hears that the study was conducted. Challenge studies in children with the vaccine strain and adults with wild type H1N1 support that activity.

In addition to that, previous field studies with the predecessor cold adapted vaccines that were done in various settings, including a Kathy Edwards site and by Kathy Edwards, demonstrated the H1N1 efficacy in that population.

And lastly, we've also been able to demonstrate comparable efficacy after annual revaccination in the AV006 study.

I'm going to turn now briefly to a discussion of the safety data and specifically initially one should remember that the safety population that's included in this analysis include approximately 16,000 healthy adults or healthy children, rather, and there are about 3,000 who were revaccinated.

The population includes approximately

4,000 healthy adults in the safety database.

What I'm going to review for you is the general safety of FluMist, including the SAEs and mortality, reactogenicity, and medically attended events, and then specifically turn to the issue that were of interest to the VRBPAC last time, particularly asthma and wheezing and the other issues that are listed on this slide.

First of all, from the big picture perspective, we're looking here at mortality and SAEs. There were two unrelated deaths in the 20 studies that were submitted for consideration in this BLA in the FluMist group. Both of those deaths were unrelated to the vaccine. One was a drowning in an adult, and the other one was a posterior fossa tumor in a child.

The SAE rates that you see here were low and similar in the FluMist and the placebo group. These are the SAE rates for children, percentage of patients with SAEs for one to four years, five to 17 years, and the entire pediatric population, as well as in open label trials. These are placebo controlled trials. These are open label trials for reference.

For the adults the SAEs are broken down

by 18 to 49, 50 to 64, and 18 to 64, with the open label studies over here.

There was a numerical increase or numerically higher percentage of SAEs and placebo controlled trials in 50 to 64 year olds. Those are completely explained by accidental injury, hospitalization for previous illness or surgical hospitalizations, and so we saw no difference in any of the age groups for SAEs.

The next series of slides are going to consider reactogenicity events, both in children and in adults, and what we've plotted here are the percent of patients with these solicited AEs or reactogenicity events for children within ten days of a vaccination.

And here what is presented in dose one. In the placebo controlled trials, that included children between 12 and 71 months of age.

Here what we see are across the bottom of the slide various reactogenicity parameters: cough, runny nose, sore throat, et cetera, various measures of temperature, and a constellation of symptoms included in the CDC-ILI definition is listed at the end of the slide.

What we see here are the reactogenicity

events collected on diary cards, and you can see that there was a small, but statistically significant increase in mild URI symptoms after dose one. When you look at the constellation of these symptoms and think about them in terms of CDC-ILI definition, for example, there was no suggestion of an increase or statistically significant difference in those parameters.

And if you think about temperature as one of the measures of severity of reactogenicity events, there were no differences between the two groups in terms of temperature greater than 101.

If you look at the adult pattern for the same reactogenicity events here for seven days, which is how they were collected on diary cards through the studies that collected reactogenicity, one sees that there's a slightly different pattern of the type of events. Some were events in which adults report rather than children, like sore throat or those sorts of things, but basically there was the same sort of pattern of mild URI symptomatology that was increased following FluMist administration.

But when you look at fever, there was no difference between the two groups whatsoever, and when you look at constellations of symptoms that are

a surrogate for sort of looking at flu-like illness, those rates were extremely low and comparable between the two groups.

Now, another measure of looking at severity of reactogenicity events is to look at the medication use, and so we looked at medication use within the ten days of the vaccination period or the reactogenicity period for children here. What you see is a small increase. The delta here is 5.3 percent of anti-pyretic analgesic use within the ten days post vaccination in children, and you see no other differences in any of the other rates.

These differences were not seen after dose two. I should mention that after dose two the reactogenicity events were actually quite a bit lower, and there were no statistically significant differences in that population.

This is the parallel medication use slide for adults within seven days of the reactogenicity period, and here you see no differences between the two groups, and FluMist was not associated with an increase in medication use in adults.

Now, of interest here are age groups of children, and so we looked at the reactogenicity

events that are included in children between 12 and 59 months of age, and between 60 and 71 months of age in the various studies, and what one sees is that, in fact, in the older children there were no statistically significant differences between any of the reactogenicity events, and overall the reactogencity events were lower in the children that were 60 to 71 months.

This is the comparable slide for adult breakdowns by age, and here you see 18 to 49 years of age and 50 to 64 years. You can see here that the pattern of adverse events or reactogenicity events in the population of 50 to 64 year olds was either similar or lower to those of the younger adult population.

Another topic of interest for deliberation is the safety of annual revaccination, and the primary data for that comes from the AV006 trial, and what we show here are children who receive -- this is a cohort of 642 children who received annual revaccination for two years within AV006 and then ultimately for a third year in an extension trial of AV006. These are the same children who received the vaccine in each of three consecutive years.

And what you see is a pattern of reactogenicity events that were lower on annual revaccination. The reactogenicity profile was similar during the second and third year of annual dosing, and overall the rates were somewhat lower compared to the primary immunization.

So from a reactogenicity perspective, I think we can say that FluMist is associated with mild URI symptoms in both children and adults; that there was no significant increase in acute influenza-like illness associated with the administration of the vaccine; and there was no increase in fever greater than 101 following FluMist administration in either children or adults.

Reactogenicity events were lower following annual revaccination.

I'm going to turn for a moment to medically attended events, and these events are seen primarily in the large safety study, AV019, which was conducted by Steve Black at Northern Kaiser in California.

In this study, this was a randomized, double blind, placebo controlled trial. It looked at the safety of FluMist in approximately 9,700 children. There were two doses given between one

and eight years and one dose in nine to 17 years of age. The outcomes were ascertained from the diagnoses in the HMO database, and the primary outcomes were medically attended events and SAEs within 42 days.

This study made many comparisons. The comparisons were all of the diagnoses identified in the HMO database by setting dose, age group, and diagnosis, and there were more than 1,500 comparisons that were made in this analysis without statistical adjustment.

What you see here are the settings in which the evaluation was conducted: emergency room visits, clinic, hospital, and combined settings; dose one, dose two, and combined doses.

And then for pre-specified age groups in the protocol one to 17, one to eight, nine to 17 years, and then 18 to 35 months and 12 to 17 months.

What you see here are some of the prespecified group diagnosis results, and what you see are acute respiratory events, systemic bacterial infections, acute gastrointestinal events, and rare events potentially related to wild type influenza and what we show in many of these and the subsequent slides are the actual occurrence in the FluMist and

placebo group, the calculated rate per 1,000 patient months, and the binomial relative risk with 90 percent confidence intervals, and in these studies the lower bounds of the confidence interval of one or above one is considered statistically significant.

So in these group diagnoses we saw no significant increases in any of those events associated as a medically attended event in the Kaiser trial.

Now, as I said, there were a number of analyses that were conducted during these studies, and when you look through all of the MAE analyses, here were essentially 14 MAEs, or medically attended events, diagnoses that were statistically significantly increased in the FluMist group and 21 that were decrease in the FluMist group.

So there are multiple comparisons. It's expected that you're going to see some of those comparisons by chance alone.

We then went through all of the event rates that were higher in the FluMist group, and when you did that and looked through the analysis of both temporal distribution as well as what the events were and other analyses, one identified three

events for which the rate was significantly increased in the FluMist group. There was biological plausibility associated with the event, and we could not exclusively exclude a cause and effect relationship for those events, and those are primarily your eye events, musculoskeletal pain events, and asthma.

These are the actual results of the MAE analyses for the prespecified diagnoses within the Kaiser trial, and what we see is here are the upper respiratory tract infection events between one to 17 years, one to eight years, 18 to 35 months. These are prespecified age cuts in various settings, as I mentioned earlier; doses, either one or combined; and the rates and binomial relative risk.

So we saw statistically significant increase, but low rate events, low difference events between the two groups for upper respiratory tract infection and musculoskeletal pain. These are both events that we saw as reactogenicity events in the reactogenicity analyses.

When you look, for example, for URI among these various age groups, and particularly for the group of interest, which is five to 17 years in the combined settings and combined dose, one sees a

rate of 25.4 percent in the FluMist group and 29.9 percent in the control group.

So clearly, as a medically attended event there a measure of, an additional measure of severity of reactogenicity. We didn't see any differences in the age group of interest for that particular event.

And the story was a little bit different in terms of asthma and wheezing, where here what we saw was for the designated term "asthma" in the database, we saw between 18 and 35 months of age in the settings of the clinic or dose, and this is mostly driven by the dose one results. One sees in terms of the rates and binomial relative risk statistically significant differences in this population.

And when you look more carefully at those populations, there still is an issue that we'll speak about in terms of a potential signal.

So we've identified a potential signal in this kind of study. The study was not obviously designed specifically to look at asthma and wheezing or those types of outcomes, and so we looked further, particularly in this population, for other evidence of an issue.

What we did were several analyses. First of all, we searched the database and the medical records for a variety of things. First of all, to identify the fidelity of the use of the term "asthma" and "wheezing" in the population. And what I mean by that is that obviously what we designated as being significant in the Kaiser trial was the specific term "asthma." And as we all recognize, particularly in young children where there are intercurrent illnesses that are associated with wheezing and where the diagnosis of asthma is actually usually not made until a little bit older, in the older age group, we look to see what the fidelity of the use in the database was.

And as expected, we saw that there was overlap between the term "asthma" and wheezing, particularly in the youth children. So whether the analysis is asthma plus wheezing or asthma alone, which was where the signal was initially identified, is the issue here.

We also assess the circumstances of medically attended events, and we look to identify in the younger children particularly whether the signal that we were seeing was related to whether or not they had a prior history of asthma and wheezing.

In this trial, the children with asthma and wheezing or particularly with asthma were excluded based on the parents' recognition of a diagnosis of asthma specifically in their child. So clearly, because of the overlap and because of the use of the terms, it is not unexpected that a number of children were in the trial who were recognized in the database as having had some previous episode of either wheezing or asthma, but the parents may not have recalled that asthma typically was the diagnosis that was given to the child.

So we looked in these additional analyses using the asthma term alone or asthma wheezing and outcomes. We looked by cumulative six months age groups. So we began at the younger age group and looked cumulatively across the age to see whether we could identify a place where the signal was detected.

We looked at dose one and dose two and across the younger age groups with history positive and history negative children. These were another 800 analyses that were done in the Kaiser study, and what we identified was only one cumulative age analysis from AV019 which was statistically significant. That was the 12 to 59 age group,

depending on how you look at it. Sometimes it was 12 to 53, the conservative 12 to 59 group.

For the whole population using asthma as the diagnosis, it had a relative risk if 3.53 and a lower bound of the confidence interval of 1.1.

When you combine terms and use more inclusive terms, such as asthma and wheezing combined, the relative risk declined to 1.58, and that difference was not statistically significant.

If this signal in the overall population is correct, the absolute increase in the FluMist group between 12 and 59 months is approximately .4 or .5 percent increase if the signal is correct.

And we also looked carefully at the group above 60 months to be sure that there wasn't a signal that was there. We looked across 60 to 107 months, which is the eight to nine threshold when one or two doses are given and all the way up to 17 years in which we found no increases in the relative risk. All of these relative risks are less than one, and none of them were obviously significant.

So that we found no signal in the children who were equal to or greater than 60 months.

When we went back to explore in the

younger children the question of whether or not this was an event that was isolated to the history positive children, what we found was that as we looked at history positive patients we saw increased relative risks. None of these were statistically significant compared to the history negative children, but in both groups there were increases in the relative risks in the population.

As expected, the delta rate, the change in the rate was higher for somebody who had a prior history of wheezing compared to somebody who did not, and so fundamentally we saw no significant difference, but increased relative risk in both the history positive and history negative children. The absolute rate was higher in the history positive children.

We also then looked at the other studies from which we can gather data related to asthma and wheezing. In AV006, the pivotal trial, we looked for cumulative age analyses and identified no significant increase for asthma and wheezing in these type of analyses in that trial.

AV012 was a large field trial of FluMist safety. It is a non-placebo controlled trial in which the comparative analysis is the pre-

vaccination period with the post vaccination period, and I think that while the interpretation, because of some issues related to the methodology comparing the pre and post vaccination period are complex, I think what we can say is that the rates from AV012 in the population of interest was not inconsistent with the rates that we saw with AV019 in the younger population. The rates were similar to the FluMist group in the AV019 patient population.

So I think what these trials tell us is that primarily AV019, which is the largest in placebo controlled trials looking at these issues, is sort of the primary place in which we can explore the issue of asthma and wheezing.

From the perspective of hospitalizations, there were two children that were hospitalized for asthma and wheezing. One of them was in the FluMist group in AV006, who was hospitalized for a day. The other was a placebo child in AV002, who was hospitalized twice for a day. Both of these children had a history of asthma.

There were no hospitalizations in the AV019 population for asthma. The events that were recorded were events that were out-patient visits or

emergency department visits. Those visits were associated with medication use at the time of the visit.

So from an asthma and wheezing perspective, I think we can say that among all of the analyses of large placebo controlled trials in children, a statistically significant difference was observed in AV019 only, and that the children for children 12 to 59 months, the relative risk was 3.53 for asthma. The rate was higher for history positive children compared to history negative children, and we didn't see a signal in the children that were greater than 60 months of age.

I'm going to turn very briefly to the issues of some of the other open issues that were discussed during the last VRBPAC meeting. From the perspective of conjunctivitis, this was an event that was evaluated in AV019. Conjunctivitis, we identified a temporal association with vaccination within the first 14 days.

What you can see here is a statistically difference for the 25 to 48 month category, but not any other age groups, and for children that were above 60 months, there was an increased relative risk, but not statistically significant.

If you take this relative risk and look for what the impact of that is, it's about a .1 percent increase in the FluMist group in greater than 60 months. These were all mild, self-limited episodes of conjunctivitis.

Pneumonia was a topic of considerable discussion at the last VRBPAC meeting. I think that what we can say now is that FluMist was not associated with an increased risk of pneumonia. These are the rates of pneumonia in the all pivotal trials for both the FluMist group and the control group or the placebo group for all pivotal studies, for children and for adults, and you can see that there are no differences between the groups across the studies for pneumonia.

So that across the final analysis data set there was no increased risk of pneumonia in those children or adults.

We also assessed the risk of CNS events. We saw no. In all of the studies we saw no cases of encephalitis, Guillain-Barre, Reye's Syndrome, or other rare disorders that are associated with wild type flu. Other CNS events occurred at a low rate. There was no significant difference in CNS events in AV019 within the 42 day period. The events that

were recognized were essentially seizures or seizures associated in a child with epilepsy, and the rates were comparable in the FluMist and in the placebo group.

Concurrent immunization was also a topic of discussion at the last VRBPAC meeting. As Jim alluded to, they are currently excluded from the proposed label, and with the indication requested being five years of age and older, the logistics and management of concurrent immunization is deemed not to be a significant problem in that age group.

We are very much committed to doing the additional trials of concurrent immunization in children. We have an ongoing trial of MMR and VARIVAX. That trial, which was reported at the last VRBPAC, is now fully enrolled with 1,251 children, and we have a number of other trials that are planned and are in discussion with CBER for other childhood vaccines in the younger age group.

Lastly, I just want to turn to the issues of vaccine virus shed, of the shed of vaccine virus, as well as vaccine virus transmission.

As Jim mentioned, there's considerable amount of evidence from the predecessor cold adapted vaccine to suggest the following challenge. The

percent of patients that shed virus, the mean peak titer, and the mean duration of shedding are all higher for young children than in adults, and that's the data that's shown here.

In addition to that, the human infective dose 50 is lower for young children compared to adults.

The data that we have regarding transmission and virus shedding, the characterization of shed viruses come primarily from the Finnish day care trial. This is a study that was conducted by our partners in FluMist, Wyeth, and was a double blind, randomized, placebo controlled trial that was conducted in 197 children, age eight months to 36 months.

These children, there were 98 FluMist patients and 99 placebo patients. Out of these 99 placebo patients there were 93 of those, that is, there were six children who were not in a play group with a vaccine or with a vaccinee. So those children were obviously not available for FluMist transmission, and the analyses are conducted with 93 patients in the placebo group.

This trial was conducted in 51 play groups in two cities in Finland. Forty-five had

both vaccine and placebo children in the play groups were physically in separate buildings in two cities in Finland. So they were geographically distributed separately from each other.

The other two that were in the same building were physically separated play groups, and there was little chance of commingling of the participants of the staff.

There was an average of 4.1 study children per play group, and the children attended day care for at least three days a week for more than four hours a day.

Each placebo trial was exposed to an average of 1.9 vaccinees.

Now, I know that several of you have been involved in doing day care studies in the past and recognize the difficulty and complexity of doing these kinds of studies. Obviously these children and families had to agree not only to either be part of the trial, but had to agree to be in the day care while the trial was being done.

This trial is actually one of the largest and most comprehensive studies of its type. It is actually in size secondary to only Gelfand's study of oral polio transmission.

The trial involved nasal culturing the first two days after dosing and at least three times a week for three weeks. So the trial itself did about 2,000 cultures, which represented approximately ten cultures per child.

There in addition to that was extensive phenotyping and gene typing of the isolates that were identified.

It's also important to recognize that this setting was designed to maximize the chance of vaccine virus transmission. One wanted to be able to detect transmission so that we identify and calculate rates, and this is a setting in which we maximize the transmission using in this setting young children who are seronegative generally and children who had extensive exposure to each other.

The statistical methodology that was used in the final analyses of the Finnish day care study was the estimation of the probability of transmission using the Reed-Frost model, and it's important to note that this model takes into account the number of vaccine-placebo interactions.

So when you're dealing with transmission rates, it's important to approximate the number of people in each of those groups, not simply the

attack rate in the population.

What we found were that there were 80 percent of vaccine recipients that shed virus. Thirty-two percent shed H1N1; 12, H3N2; and 74, Type E virus.

The mean duration of shedding in days was 7.6 days. There was one placebo child who shed Type B vaccine virus on the day 15 visit, and using the Reed-Frost model for that documented case of vaccine virus transmission, the probability of transmission was .0058 with the upper bound of .017.

Now, in addition to that, there was wild type A H3N2 circulating the community in Finland during the time the trial was conducted, and there were six additional placebo children who shed Type A influenza virus during the study. Two of them shed wild type A strains and did not shed vaccine virus. So those are clearly not vaccine virus transmission.

There were four additional patients, placebo patients, who shed a Type A virus that was isolated and identified in Finland, but could not be reisolated and identified and thus could not be confirmed to be either wild type or vaccine virus.

Let me walk you through those four cases. The first one we consider to be a possible

case of vaccine virus transmission. That child shed on one day in a play group where one vaccinee shed vaccine virus seven and ten days earlier.

So although it couldn't be identified as vaccine or wild type virus, it's possible that that was a vaccine virus transmission.

There are two cases which we would consider to be highly unlikely to be vaccine virus. The first one was a patient, a child who shed on two occasion. The first was before any vaccination occurred in the play group. That's most likely wild type virus, but we couldn't totally exclude that it was vaccine virus.

And the second time they shed was a few days latter, which was one day after the vaccine was introduced into that play group. So clearly, again, this is unlikely to be vaccine virus.

The other unlikely case was a child who shed on one occasion. There was no other participant in that play group who shed Type A virus, but there was one who shed B virus five days earlier. So other A shedders in the population, and the isolate from that patient was a Type A virus.

And we consider the fourth patient really not possible because that child shed two days

before vaccine was introduced at all into that play group.

If one calculates the probability of transmission based on the Reed-Frost calculations, you see that using the confirmed case I've showed you that transmission probability. If you add the one possible case, the probability of transmission is .01 and the possible plus the two unlikely cases is .02.

And we also did extensive virus characterization of the shed viruses. The temperature sensitive and cold adapted phenotype was confirmed in all of the isolates that were tested. There were 124 isolates in this trial that were tested to confirm this.

In addition to that, we took the last isolate from each of the children that we had isolates at that time available for those, and we chose the last isolate so that it was farthest away from the introduction of the vaccine, and we completely sequenced 55 of the shed isolates.

There were no reversions of the master donor virus attenuating mutations. As expected, there were a minor number of mutations that were observed in influenza. That's not unexpected.

And if we took viruses t hat contained the mutations that were observed in more than one of the isolates and put them back into ferrets, they all retained the attenuated phenotype.

When we look at the transmitted virus, that retained the 6:2 genotype. It was identical in genetic sequence to the virus that was shed by the vaccine recipient in the play group. It retained the cold adapted and temperature sensitive and attenuated phenotype. It was not associated with increased reactogenicity, and was not observed in any of the other placebo members in the play group.

So I think we can conclude from the Finnish day care study that in this day care setting the probability of transmission was estimated to be .006 or .02. There was no phenotypic or genotypic reversion observed in the shed or transmitted viruses.

So, in conclusion, we believe that we have demonstrated the efficacy of FluMist in the prevention of culture confirmed influenza in children. Efficacy was consistent across all the age groups that were studied, and the efficacy in children greater than or equal to 60 months was similar to the group as a whole.

Effectiveness of FluMist was demonstrated in trials in adults. The effectiveness was consistent also across age subgroups, and we found no evidence of the 50 to 64 year olds being significantly different from the population as a whole.

Efficacy was comparable on annual revaccination.

We believe that FluMist is safe in children greater than or equal to 60 months through 17 years of age and healthy adults in 18 years through 64 years of age.

There was a mild increase in self-limited URI symptoms, but no increase in fever greater than 101 or composition of symptoms that would constitute influenza-like illness.

We saw in adults the safety profile consistent across age groups, including in the 50 to 64 year olds.

We believe that additional information is needed to assess the risk-benefit in children under 60 months. We identified a possible signal in that age group and consequently need to collect additional information in that pediatric age group.

We believe that the safety profile was

similar and the events were lower on annual revaccination, but the risk of vaccine virus transmission is low. The probability is estimated in the day care center, and those rates are likely obviously to be lower in older children and in adults.

And we've demonstrated genetic and phenotypic reversion has not been observed in the studies that we've done so far.

So we present that data to you as well as the data from the previous VRBPAC presentation as a portfolio of information to support the proposed indication, which is for active immunization and the prevention of disease caused by Influenza A and B in healthy individuals age five years through 64 years of age.

We believe the FluMist represents a potentially important addition to the portfolio of the public health armamentarium, as well as the medical armamentarium for both increasing the rates of influenza immunization, as well as for prevention of flu in the population in the United States.

Thank you.

CHAIRMAN DAUM: Thank you, Dr. Connor.

What I'd like to do now is to get input

from the committee with regard to clarification of Dr. Connor or Dr. Young's presentation, things that went by too quickly perhaps or issues that you'd like to know whether there are other data about, and then we'll take a break and hear from Dr. Mink and our FDA colleagues.

So Dr. Snider first and then Dr. Edwards.

DR. SNIDER: Thank you.

I actually had four questions. Hopefully relatively short and sweet in terms of an answer.

With regard to the statement about efficacy in children greater than 60 months, in looking at the materials, I actually see up to 83 months, but I didn't see data from 83 months through 17 years of age, and I was wondering about if there are efficacy data that weren't shown on that point.

DR. CONNOR: No, the original pivotal studies were done in children who were 12 to 15 and 17 months of age, and as I said, the oldest children that were in those trials had aged up to 83 months by the time they were in the second year, but there's not additional efficacy-effectiveness data within the population.

DR. SNIDER: So we have safety data, but no efficacy data?

DR. CONNOR: That's correct. The efficacy data is in the younger children, and what we presented were data to show that the efficacy in all of the age groups that we demonstrated were consistent.

There is a fair amount of evidence, however, obviously with the cold adapted predecessor vaccines in that age group demonstrating that efficacy exists.

DR. SNIDER: Right, right. Thank you.

The second question very quickly. In adults you mentioned that they were healthy adults, but I don't recall your mentioning whether they were smokers or not and whether there was a difference in efficacy or safety as it related to smoking status, if that's known.

DR. CONNOR: Yeah, I don't. They were healthy adults from the perspective that they were healthy working adults working at least 30 hours a week. To my knowledge, there's no specific information about whether we can separate the population by whether or not they were smokers or not, and I don't think that information was

collected as part of the trials.

DR. SNIDER: Okay, and then finally, I'll run these two questions together because it has to do with adverse events, runny nose, for example, asthma, and wheezing. Is there any association between those types of respiratory events and shedding, the amount of shedding, more or less in those people or, you know, the type of strain they might be shedding? Any information that would give us a clue around the etiology?

Obviously this is not necessarily relevant to the questions FDA is posing, but interesting in terms of what the etiologies might be for these adverse events.

DR. CONNOR: Obviously because the adverse event was a post hoc sort of identified issue and studies were driven by primarily influenza diagnoses, there's not specific information that correlates shedding with those specific outcomes.

CHAIRMAN DAUM: Thank you, Dixie.

Dr. Edwards, Katz, Eickhoff, Myers, and Markovitz.

DR. EDWARDS: I have two questions for Ed. The first is that for those of us who are pediatricians, we know how extraordinarily difficult

it can be to decide whether a patient has bronchiolitis or asthma in those first few years of life, and which I would think probably complicated extensively your analysis of the wheezing episodes.

Could you tell us a little bit how you have dealt with bronchiolitis, whether the diagnosis of asthma was consistent in the Kaiser population, whether there are guidelines upon which that diagnosis is made in that population?

DR. CONNOR: Yeah, the best we could do, Kathy, is that the analyses that I included as asthma and wheezing actually include other synonyms for wheezing. So reactive airways disease, shortness of breath, bronchiolitis, bronchitis are included in that analysis.

As you mentioned, it's complicated if you just look at these are just simply illness visits. So what you're recording is what's in the record at the time that the visit occurred, and various people are seeing the child. They could have recorded that it was rule out asthma. They could have recorded a variety of different things.

So what we've tried to show you is the original signal and then the most inclusive diagnosis that we could get out of the Kaiser

database.

DR. EDWARDS: Did you extract out the episodes during times when RSV was circulating to eliminate that or was that analysis done?

DR. CONNOR: Yeah. Well, not particularly because we just basically looked at the two randomized groups. So we were assuming that the same things were happening in both of the groups and looked at the comparison between the two treatment populations.

DR. EDWARDS: You may want to subsequently look at that.

DR. CONNOR: Yeah, yeah.

DR. EDWARDS: The other question that I had relates to the challenge study, and obviously it was beautifully designed, and as I mentioned to Dr. Katz, could only have been done in Europe, but I think that the fact that it was conducted during the time of co-circulation with wild type virus may, indeed, have decreased your transmission with the vaccine strain because of interferon generation or interference of a perhaps more potent fibrous than the attenuated vaccine.

So do you have any comments or ideas about that?

DR. CONNOR: Yeah, I think the actual number of cases that were wild type flu that were identified during the transmission study were pretty low. So the expectations that while it certainly was circulating and could interfere with the interpretation of at least those cases that we were talking about, there wasn't a whole lot circulating in those day care.

CHAIRMAN DAUM: Thank you.

We move on to Dr. Katz, please.

DR. KATZ: As I should have anticipated, Dr. Edwards has asked most of the questions I was going to, but I'd add one comment. It may seem gratuitous, but the whole question of transmission, the other vaccine that we used for many years where transmission was an issue was oral polios, and it was considered advantageous that there was transmission from immunized children to those who didn't have the benefit of the immunization, and yet this was a preparation where reversion to neurovirulence was much more likely to occur than as you've been able to show with your nasal flu vaccine.

And my question was: in any of the transmitted children did anyone look at antibodies

to see if they developed an immune response as the result of transmission?

DR. CONNOR: That wasn't looked at, Sam, in the one kid who we know transmitted the virus.

CHAIRMAN DAUM: I have Drs. Eickhoff, Myers, Markovitz and Diaz, and then I think we'll take a break and hear from the FDA, and there will be ample time this afternoon to return to many of these issues as per the committee's pleasure.

Dr. Eickhoff, please.

DR. EICKHOFF: Thank you.

The concurrent vaccines trial, the MMR and varicella vaccine trial, what age groups are those children? I understand the trial is now fully enrolled.

DR. CONNOR: We're now halfway enrolled. The age group is between 12 and 15 months. So they're the younger kids.

DR. EICKHOFF: That leads me to the second question, which is if you could share with us to the extent that you're able your long term plans about that 12 to 49 month age group.

DR. CONNOR: I think obviously we're very interested in understanding the issues that pertain to that population. As I mentioned, we have

fully enrolled the trial that was the MMRV trial.

In addition to that, we have trials designed and in discussions with CBER to begin to look at the other vaccine components so that for all of the other childhood vaccines -- and obviously we'll have to go back and look at the issue of the signal of the asthma-wheezing issue in that population.

We have ongoing trial a study with Steve Black and Kaiser trying to sort out are there better tools to be able to distinguish history positive and history negative children. This trial obviously just used parental history of asthma or the parental report of a history of asthma in the child as the discriminator.

We're also going to be looking at other studies in that group of children.

DR. EICKHOFF: Kindly could you again share with us your thoughts about the other end of the age spectrum? I remember, oh, ten years ago, I think, or more, I think, John Traynor's study from Rochester and the apparent perhaps not synergistic, but both vaccines were better than either one alone.

This may not ever fly as public health policy with regard to influenza vaccine, but if you