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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OPEN SESSION

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THURSDAY,
JULY 26, 2001

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The Committee met at 10:55 a.m. at Gaithersburg Holiday Inn, Two Montgomery Village Avenue, Gaithersburg, Maryland, Dr. Robert S. Daum, Chairman Presiding.

PRESENT:

Robert Daum, M.D.	Chairman
Nancy Cox, Ph.D.	Temporary Voting Member
Kathryn Edwards, M.D.	Temporary Voting Member
Theodore Eickhoff, M.D.	Temporary Voting Member
Walter L. Faggett, M.D.	Member
Barbara Loe Fisher	Member
Diane E. Griffin, M.D., Ph.D.	Member
Samuel L. Katz, M.D.	Member
Steven Kohl, M.D.	Member
Martin Myers, M.D.	Temporary Voting Member
Geoffrey Schild, Ph.D.	Temporary Voting Member
Dixie Snider, Jr., M.D., Ph.D.	Member
Mark Steinhoff, M.D.	Temporary Voting Member
David S. Stephens, M.D.	Member
Nancy Cherry	Executive Secretary

OPEN

C-O-N-T-E-N-T-S

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

(10:55 a.m.)

CHAIRMAN DAUM: Good morning. I'd like to welcome everyone to the continuation of our meeting this morning. I'd like to welcome both committee members, consultants, sponsors, FDA folks and other interested parties. I would like to ask everyone to remember that the purpose of this meeting is to hear information and discussion and allow committee members to deliberate and provide advice to the FDA.

In order to do that, I would very much appreciate it if cell phones, beepers and other disrupting devices be turned off now, so that we don't have to deal with them as we go along. I think that we will now turn the floor over to Nancy Cherry who will read the committee conflict of interest statement.

MS. CHERRY: Well, good morning, welcome to all of you. I think they're probably in the process of finding chairs for any of you that don't have chairs. It looks like most of you found seats. A couple of announcements; first of all, if there is anything we can do for particularly the committee but also for any of you, the committee management specialist who put together the meeting is sitting at

the desk out front. That's Denise Royster. She's assisted today by Rosanna Harvey. Tomorrow she will be assisted by Sheila Langford. Actually, Denise is in the room at the moment, but anyway. Now, I'll read the statement.

"The following announcement addresses conflicts of interest issues associated with the Vaccines and Related Biological Products Advisory Committee meeting on July 26th/27th, 2001. Of the Advisory Committee Members, Drs. Manley, Kim and Diaz could not be with us today or tomorrow. The Director for the Center for Bioligics Evaluation and Research has appointed Drs. Nancy Cox, Kathryn Edwards, Theodore Eickhoff, Martin Myers, Geoffrey Schild and Mark Steinhoff as temporary voting members for the discussions on Friday, July 27th regarding safety and efficacy data as well as the proposed indication for Aviron's FluMist™.

To determine if any conflicts existed, the Agency reviewed the submitted data and all financial interests reported by the meeting participants. As a result of this review, the following disclosures are made regarding the discussions today and tomorrow, July 26th/27th. Dr. Stephens and Edwards have each been granted a waiver in accordance with current

statutes, which these waivers permit them to participate fully in the discussions. In addition, Dr. Brian Murphy has been granted a limited waiver which will permit him to make a presentation and answer any questions related to that presentation.

Doctors Daum, Goldberg, Griffin, Kim, Kohl, Snider, Stephens, Edwards, Eickhoff, Cox, Myers and Steinhoff all have associations with firms that could be or appear to be affected by the committee discussions. These involvements have been reviewed, and in accordance with current statutes, it has been determined that none of these is sufficient to warrant the need for a waiver or an exclusion. In the event that the discussions involve specific products or firms not on the agenda and for which FDA participants have a financial interest, participants are reminded of the need to exclude themselves from the discussions. Their refusals will be noted for the public record or their disclosures will be noted for the public record.

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

waivers addressed in this announcement are available by written request to the -- under the Freedom of Information Act". And we do have one disclosure to be made today.

DR. MINK: I am Dr. ChrisAnna Mink. I am the medical reviewer for this BLA. I joined the review team in January of 2000 and would like to disclose the prior to joining the FDA, I worked as a consultant for Aviron for approximately 40 hours. I had not performed any consulting activities for Aviron for more than one year prior to my joining your review team.

My prior association with Aviron was disclosed to the FDA Ethics Office and their review deemed there was no conflict of interest from my participation.

CHAIRMAN DAUM: Thank you, Dr. Mink.

DR. MINK: Oh, it was January of 2001 that I joined the review team.

CHAIRMAN DAUM: Thank you again, Dr. Mink. I would like before we start, Dr. Patriarca's presentation to ask the committee members and consultants to briefly identify themselves. Dr. Snider, We'll start with you and just go right around.

DR. SNIDER: Dixie Snider, Associate

Director for Science, Centers for Disease Control and Prevention.

DR. KOHN: Steve Kohl, Oregon Health Science University.

DR. FAGGETT: Walt Faggett, Pediatrician in the National Medical Association, Pediatric Section.

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

MS. FISHER: Barbara Loe Fisher, President of the National Vaccine Information Center.

DR. STEPHENS: David Stephens, Emory University.

DR. GRIFFIN: Diane Griffin, Johns Hopkins.

DR. KATZ: Samuel Katz, Duke University.

DR. SCHILD: I'm Geoffrey Schild, from the U.K. National Institution for Biological Standards.

DR. COX: Nancy Cox, CDC.

DR. EICKHOFF: Ted Eickhoff, University of Colorado.

DR. MYERS: Martin Myers, National Vaccine Program Office.

DR. EDWARDS: Kathy Edwards, Vanderbilt University.

DR. DAUM: And I'm Robert Daum from the University of Chicago. I'll maybe ask the FDA folks who are seated at our table extension to identify themselves also.

DR. LEVANDOWSKI: Roland Levandowski, I'm with the Division of Viral Products at CBER.

DR. MINK: Dr. Chris Mink. I'm with DVRPA and CBER.

DR. GEBER: Antonia Geber, CBER.

DR. RIDA: Wasima Rida, Division of Vital Statistics, CBER.

CHAIRMAN DAUM: Thank you all very much. AT this point I'd like to turn the floor over to Dr. Patriarca as we begin the formal part of the session and have the introduction to the session and summary of prior VRBPAC deliberations. Peter.

DR. PATRIARCA: Thank you, Dr. Daum. Good morning everyone. Can you hear me okay? Does this mouse work? Okay, thank you.

Good morning, the topic of the meeting today and tomorrow involves FluMist™ or as generally known live, that is to say a vaccine that depends on active viral replication in order to be effective, attenuated, that is to say the production of illness on the milder end of the spectrum in comparison to the

wild-type, cold-adapted and temperature sensitive which in essence means that the replication of the virus is restricted primarily to the nasopharynx, trivalent, meaning that it has three components, two Type A and one Type B, an influenza virus vaccine.

The vaccine is actually made by crossing what is known as a Master Donor Virus with a wild-type virus by co-infecting embryonated eggs. The results of this, ideally, is what is known as a 6:2 reassortant, meaning that the internal genes are derives from the Master Donor which is attenuated, cold-adapted and temperature sensitive but the outer surface proteins, the hemagglutinin and the neuraminidase, which are important in immunity, are derived from the wild-type virus of interest and of epidemiologic importance.

The vaccine, again, is a trivalent preparation. The virus is diluted with normal allantoic fluid, that is to say more or less egg whites, and it is instilled into the nose rather than being injected as other influenza virus vaccines are. I have three purposes this morning. One is to orient the Committee and the audience to the presentations that will follow mine. Secondly, I will focus on some risk/benefit considerations and in particular those

that may not be emphasized later on today. And then importantly, I'm going to review some of the deliberations that took place approximately three years ago in reference to quote, unquote, "generic" live attenuated flu vaccines, but which also included some specific discussions about FluMist™ and its predecessors.

In talking about the potential benefits of the vaccine, this can be made fairly obvious simply by looking at the risk of wild infection. As I believe everyone knows, influenza is the most common cause of medically attended acute respiratory illness in all age groups. There is also a high risk of mortality and other severe complications, particularly in the elderly and other medically risk populations. And I think very importantly there was the recent, what I term rediscovery of the clinical and public health importance of influenza in children, particularly those age zero to four years.

There have been a number of recent studies which show that particularly among high risk children in this age group, they have a rate of about 500 excess hospitalizations per 100,000 and even healthy children have 100 excess hospitalizations per 100,000, and these are approximately four times the rate of

other age groups. So, clearly, the impact of influenza in this country and elsewhere is enormous.

Now, it's important when we talk about FluMist™ that there are some special challenges that pertain to this particular vaccine and vaccines like it that don't necessarily apply to other vaccines. First of all, again, to emphasize that this involves the purposeful administration of a live replicating agent and indeed, the vaccine will not work unless it replicates. Secondly, we're talking about an unusually large target population. And, in fact, Aviron has requested an indication for persons age 1 to 64 years, which in this country is in excess of 200 million.

Thirdly, annual vaccination is required. In contrast to the other vaccines other than inactivated influenza vaccine which generally require only a few doses or a series of doses with periodic boosters, this will require annual vaccination. Next, annual reformulation is very likely because the influenza strains, as everyone knows, tend to change over time and it's very likely that the vaccine will vary from year to year. and then finally, there is, as everyone knows, a licensed product specifically inactivated influenza vaccine, which has been licensed

in this country and used for approximately the last 50 years which does have a very long-standing history of safety and efficacy.

Now, talking in general terms about live virus vaccines, one can think of the risks and benefits utilizing a matrix and in this matrix on the vertical access, we have risks at the bottom, benefits at the top and then we have four components to this, each of which contribute some degree of risk and benefit. The first are the vaccine strains and the cell substrate used to produce the vaccine. The second component is the manufacturing process and the consistency of that process. The third is what happens to the host, the vaccinee and then particularly with a live vaccine consideration has to be given to the potential for transmission of the vaccine to other people. So let's take these in order.

As far as the benefits are concerned, what this vaccine is intended to do is to provide an antigenic stimulus to the immune system to produce the appropriate immune response and with this live virus vaccine, it is intended to produce an immunity which is very similar to natural infection which, of course, goes beyond the immunity that's induced by the

inactivated vaccine and this immunity ideally is both homologous, that is against the virus to which you're being immunized, but also some heterologous protection, that is to say some cross-protection with variance that might be closely related.

Now, on the risk side, though because this is a live product, it will necessarily contain some degree of reactogenicity as you will hear later on today and importantly it also carries a risk, particularly in a live product, of carrying exogenous or endogenous adventitious agents. And with this vaccine, it's important to point out that whereas the vaccine is produced in eggs which are known as specific pathogen free eggs, the wild virus donor is not necessarily and in most cases will not be obtained from one of these eggs.

In other word, these isolates come from Asia and from clinics all over the world and generally the, if you will, run of the mill eggs are used for the isolation of those viruses, so there is some possibility then, that these agents could be transmitted and end up in the vaccine.

Now, with regard to the manufacturing process, it's particularly critical and especially for this vaccine, which has the chance of changing every

year, that the purity, potency and consistency, this is sort of the triumvirate of every vaccine, are very closely maintained. And so these three components are essential.

On the risk side, there's always the risk of contamination during the process of manufacturing and importantly for this vaccine, one is concerned about genetic instability. Influenza is a very highly mutable virus and if certain changes occur in the genetic constitution, it could have an adverse effect on attenuation and attenuation is a very key word that we'll talk about repeatedly today that should be kept in mind by everyone and there may also be some changes in antigenicity.

There is also a residual cellular DNA that can come from the cell substrate, in this case the eggs and also residual egg protein to which, as everyone knows, a small percentage of the population is allergic. In considering the host response, I've already mentioned that influenza virus vaccine and as you will hear later today, this also applies to this vaccine, has a very large potential to substantially reduce infection, due to wild-type virus, shedding, once wild-type virus exposure occurs, and importantly, illness, complications and mortality.

On the other hand, there are also some adverse effects that can occur with the host response. These include both acute and delayed adverse drug reactions. There is the potential for reversion of this virus, a change in the attenuation properties of the virus. There's also a possibility of immune selection, that meaning that this virus may not necessarily induce heterologous protection but rather just amplify the homologous response or previous response that the recipient may have had to a prior influenza infection. There's also the possibility of immune interference between the types of the vaccine and this will be discussed a little bit later on, and then finally there is concern about allergic reactions, again because the viruses are diluted with normal allantoic fluid that is administered intranasally.

The final component, transmission to contacts, it has been arguably stated with oral polio vaccine being the prototype, that immunization -- that indirect immunization is actually a positive benefit of a live virus vaccine. But in this case, in the influenza case, this is probably not a desirable property and this is for two reasons; one, there might be a greater chance of reversion in the virus, that is

to say a switch to a more virulent form once its passage in humans, if you will, rather than eggs and there is also a possibility of reassortment with wild-type virus.

And these are respects and particularly genetic instability, attenuation that will be covered in detail by Dr. Murphy in a few moments. Now, in November of 1998 this committee met and there are some persons still on the committee from that time, and we do have also some cross-overs of some of the consultants. And in that meeting, there was a discussion about quote, unquote "generic" considerations pertaining to live attenuated influenza vaccines, not necessarily just FluMist™ and there were four main topics that were discussed.

One has to do with containment of the virus basically at the manufacturer's site. Second has to do with the maintenance of attenuation of the vaccine virus, third the potential for the vaccine virus to reassort with wild-type influenza viruses and then finally the risk of allergic reactions due to primarily the administration of egg protein but also the potential risk for bacteria super-infection. What I'd like to do now is quickly go over these four things in a slightly different order.

The first thing I'll talk about is containment. The issues involved here are the potential release of essentially the Master Donor Virus which is an H2N2 virus. Some of you may remember this as a so-called Asian influenza that circulated between 1957 and 1968 and was especially virulent, also the B Master Donor Virus which also has genetic properties that are unique to that. So what are the chances of this thing -- these viruses being released into the environment, into the general population and could that pose a problem?

Secondly, the issue was raised about the manufacturing of the live attenuated influenza vaccine that had a novel hemagglutinin or neuraminidase and this would be done as part of a pre-pandemic exercise where one might before the pandemic actually hit the United States, try to manufacture a vaccine for potential use. The opinion of the committee and the consultants was that these issues were not considered to be problematic, that these viruses had been used in a number of laboratories and manufacturing facilities now for 30 plus years and that there had never been an instance where these things were released and moreover, generally, whenever one uses either these viruses or particularly viruses with novel

hemagglutinin and neuraminidase, these require a very high level of biosafety that is very strictly enforced. So containment in the opinion of the committee at that time was that this was not a problem.

The second issue is hypersensitivity reactions and bacterial super-infection. The issues there, once again, are the repeated administration, the annual administration of egg protein intranasally which, as everyone knows, is not a natural root of exposure. This pertains to the allergic component. As far as bacterial super-infection is concerned, the concern here is that even though this is an attenuated virus, it does involve active replication. And it was shown particularly with the H2N2 virus, the wild H2N2 virus, that this virus is prone to de-epithelialize the respiratory tract. It can also interfere with ciliary function and importantly not only the H2N2 but other influenza viruses can interfere with the function of polymorphonuclear leukocytes which are very important in immunity against bacterial infection.

In the opinion of the committee at that time most people believed, although there was some question, that any egg protein administered

intranasally would probably be cleared prior to the point that the virus would actually replicate so this was not seen as a problem. And as you will hear later on this afternoon, Dr. Mink and perhaps Aviron, too, will address the issue of hypersensitivity reactions with actual clinical data.

And the other opinion regarding bacterial infections is for a variety of reasons that the committee opined that these were probably more likely to be prevented than caused. And again, there will be some information presented this afternoon regarding this. There are some data that are now coming to light.

The third issue was introduction of new viruses into the environment in the form of live attenuated influenza vaccines. The issues here, again, are the purposeful introduction of genetically modified influenza viruses into the general population and secondly the potential for these viruses to reassort with wild-type influenza viruses to potentially, potentially create more virulent human strains that have not circulated before. Now, in the opinion of the committee, they determined, and you will hear information pertaining to this today that the transmission, when it occurs, appears to be very

limited and as Dr. Murphy will talk about a little bit later, the progeny of that transmission, those viruses will also, very likely if not solely, be attenuated rather than more virulent.

Secondly, Dr. Cox may want to mention this later on, but Dr. Cox and her colleagues at CDC have been involved over the years with an extensive evaluation of another live attenuated flu vaccine in Russia derived from a strain called A/Leningrad which is different from the A/Ann Arbor that we're discussing today, but nevertheless, this has been looked at repeatedly by her group and there's no evidence at least that they've been able to determine, that there's been circulation of genes derived from this vaccine in Russia, despite having been in use for many years.

Now, despite this positive opinion, there was the lingering concern that genetic modifications cannot be ruled out and with influenza being a very unpredictable agent, in and of itself, anything can and will go wrong. So this still remains a concern and I believe that Dr. Murphy will probably also cover this during his presentation. Now, Item Number 4 was the degree to which we could be assured that this vaccine would always be attenuated no matter what the

conditions upon which it was made, no matter what wild-type virus was used.

And again, the issues are being sure that this so-called 6:2 reassortant strain, no matter what it is, is always going to be attenuated. The second concern is that animal models, to address this, particularly the ferret, traditional animal model, has been less than ideal. Part of the reason for this is that the ferret's body temperature is higher than the body temperature of a human and because the virus is cold-adapted then, and temperature sensitive, the ferret may not reveal all that you might like to be revealed in determining attenuation.

And then importantly, as is true for almost all other live attenuated vaccines, the genetic basis of attenuation is generally unknown. So n the opinion, and this is an important opinion which the committee should reconsider today, and will have the opportunity to reconsider during the discussion period, is that there was a consensus that ideally there should be annual human testing prior to widespread distribution of the vaccine. That having been said, there was also discussion of the approach and logistics and there was some wheel-spinning and no real conclusion to this was determined during that

particular meeting.

Now, it's important to know that in addition to these concerns, we also have some other issues involved with this vaccine. First, as you will see later on, there is a difficulty in assessing the true reactogenicity of this vaccine, primarily because the quote, unquote "placebo" was not an inert substance. In fact it was allantoic fluid and as you will hear later on, there was a very high degree of reactivity in the control group. Second, we have to be concerned as we do with any vaccine, about rare and uncommon adverse events. And these really fall into two categories that can really only be determined once the vaccine, if licensed, is used on a very large scale basis.

One can think about a slightly more common adverse event such as pneumonia, bronchiolitis, bronchitis, croup, sinusitis and even otitis media. But more importantly and concerning are that influenza wild-type virus infection can also lead to a series of rather severe complications. These include toxic shock syndrome, myocarditis, pericarditis, rhabdomyolysis, encephalopathy, encephalitis, Guillane-Barre Syndrome, and there might also be the possibility of developing thrombocytopenia as has been

demonstrated with MMR vaccine. This is because the virus is grown in an egg substrate. There might be antibodies produced against one of the surface receptors, the vitronectin receptor which can cross-react with receptors on the platlettes and thereby lead to thrombocytopenia. So whether or not these events will occur with this attenuated, and I have to emphasize that again and again and again that this is an attenuated virus, we don't know yet. The presumption is, is that all of these adverse events will occur at a much less frequency than it will with wild-type but that remains to be determined.

Another issue has to do with repeated and again annual dosing. There are two concerns here. One is might there be potential adverse immunologic consequences of giving a live as opposed to an inactivated virus vaccine from the standpoint of what is known as quote, unquote "original antigenic sin", also know as quote, unquote, "the Hoskins effect", which was described by a physician in England some number of years ago which basically suggested that if you repeatedly vaccinate someone that basically what might be involved is you simply reinforce the antibody response that they had to some previous infection and you don't really update their antibody very well.

Now, this issue has, in fact, been considered at great length by a working group by the ACIP and at least in the opinion of that group, this is only a theoretical concern and it not likely to be a real concern. The other issue with repeated annual dosing pertains primarily to seropositive persons and especially adults and specifically as you will hear later on, this virus replicates very poorly or even not at all in persons who have previous immunity. So the question here becomes bang for the buck. If you vaccinate people annually, if they really don't need it, and there's no way of knowing whether they need it, there will be some proportion of people then who will not have essentially any benefit but who might also have some risk associated with that. So this is also a general concern.

Two other concerns, first, as you will hear later, although the vaccine, the indication for the vaccine is for children as young as one year of age, Aviron does not yet have information on the responses when the vaccine is administered with other childhood vaccines nor to they have information on co-administration of this vaccine for travelers. Travelers is one of the indications they've asked for. Traveler, foreign travelers often receive other

vaccines but there is no information about that at the moment that has been submitted to the FDA.

And then finally, an important consideration as you will hear later, is that there's very limited experience in high risk groups. You will hear some information on HIV-infected persons. You will hear some information about small groups of asthmatics but in general there's a very limited experience in people with pre-existing medical conditions who might be more susceptible to the effects of this attenuated virus than would the normal host.

So in summary, I hope I've made it clear that the task before the committee is going to be very difficult, that this vaccine poses very complex benefit/risk considerations. These complex considerations apply not only to this committee and to us at the FDA, but also recommending bodies, the ACIP, that AAP and so on. Secondly, just to emphasize that the principal focus of today's discussion is going to involve clinical considerations and virtually all of the presentations you'll hear this afternoon will pertain to that.

I just want to re-emphasize that there are other important issues pertaining to this vaccine.

There are some manufacturing issues which cannot be discussed during this session, which are still under review and in consultation with Aviron. There's the attenuation reversion problem which Dr. Murphy will cover in great detail. I presume that he will also talk about potential for transmission and also reassortment with other viruses in nature. And then finally, just to emphasize this again, that there's very little information about the use of this vaccine in populations that are medically high risk.

Now, what I wanted to do, what I've been asked to do by Dr. Midthun is before I end, is to review the questions that the committee will hear tomorrow if that's okay, unless you want to ask me questions now and then present the questions after that.

CHAIRMAN DAUM: I think it might be nice to hear if the committee would like clarification of points that you made first, if that's okay.

DR. PATRIARCA: Okay.

CHAIRMAN DAUM: So why don't we open up your presentation to the committee at this point for clarifying questions, concerns, comments? Dr. Katz?

DR. KATZ: I don't know if this question is best addressed to Dr. Patriarca or perhaps to Dr.

Arcuri. And you've referred several times to the fact that you're concerned about allantoic fluid which is used as a diluent. Why it is used as a diluent? Is it a stabilizer or does it in some way adjuvant? What is the choice of allantoic fluid as the diluent?

DR. PATRIARCA: I'd like to refer that to Aviron.

CHAIRMAN DAUM: If we can get a response to it, that would be great. If not, we'll defer to this afternoon.

DR. ARCURI: It will be a very brief response. Basically, allantoic fluid was used as a diluent to assure a constant level of background protein so that you didn't have variation from virus formulation to virus formulation because as I said, potencies can vary, so the amount of virus you add will vary depending on the potency of the strain.

CHAIRMAN DAUM: Thank you.

DR. SCHILD: I have a question. In your presentation, you're making the assumption that every time you need to change the composition of the inactivated vaccine it will be necessary also to change the composition of the any live future live vaccine. I mean, that could be a point of discussion, whether the immunological properties of a live vaccine

differ significantly from those of an inactivated vaccine.

DR. PATRIARCA: Yes.

DR. SCHILD: Which suggests that you might change less frequently or more frequently or what?

DR. PATRIARCA: Yeah, your point is very well taken, Dr. Schild. Yeah, that's absolutely right. I don't think we know whether it will, in fact, in practice be necessary to change this vaccine just as we do the inactivated vaccine, a point well taken.

CHAIRMAN DAUM: I'd like to ask, some of the issues you raised, Peter, go to the need for ongoing interaction with the agency, the vaccine, the general public, ongoing issues but efficacy was not one of the things that you mentioned and I've actually been on my high horse a long time about what I feel is a need to have ongoing monitoring of the current influenza vaccines in terms of their annual efficacy. How do you see this new vaccine potentially as being monitored in that regard? Are there any concerns?

DR. PATRIARCA: I'll try to answer that although perhaps Nancy Cox or Dixie Snider might also want to answer that because I think this is primarily an issue which pertains mainly to CDC but the way that

we've worked that with inactivated vaccine is we now have this historical data base where there have been a number of primarily ad hoc vaccine efficacy studies that have been done over time and also a number of retrospective analyses and these analyses do give us a lot of confidence that when there is a good match between the wild strain and the vaccine strain, that the vaccine -- the inactivated vaccine has a very reproducible rate of efficacy.

The question might then be raised should another system be in place for this vaccine? Is it considered sufficiently different, how would that be done? Whose responsibility would it be to set up those studies and personally, I believe that those are issues that should be discussed by this committee.

CHAIRMAN DAUM: I would agree and maybe I will pick up the theme again when we have more general discussion. Dr. Kohl, please.

DR. KOHL: I would strongly agree with that and in terms of this committee picking up that issue and this vaccine in particular, regarding the other flu vaccines in which the indication age-wise is much broader and every year when we discuss flu vaccine we talk about the lack of good studies in children, the question of efficacy in children and

immunigenicity and it seems to me with essentially starting a new ball game here, that it's critical that we bring some of that stuff in at the beginning instead of next year and 10 years from not saying, "Gee, wouldn't it be nice if we had studies in pediatric populations and other high risk populations as well".

CHAIRMAN DAUM: Thank you, Dr. Kohl. Other committee comments regarding clarifying points with Dr. Patriarca's presentation? One last, Dr. Edwards.

DR. EDWARDS: The license application, does it state that the strain collection will be comparable to what is used in the inactivated vaccine or is that not stated in the license application in reference to your -- in reference to the comment earlier?

DR. PATRIARCA: I believe it says that the strains are going to depend on what this committee decides but I'll ask Roland Levandowski to be sure about that.

DR. LEVANDOWSKI: That's my understanding, too. I can't quote you what is says exactly in the BLA but the intent has always been that the strains that are used in the live attenuated vaccine will

reflect the hemagglutinin and the neuraminidase of the current circulating strains and that's been the strategy that's been used in producing vaccines to this point. It doesn't necessarily mean that the strain would be identical to the one that's in the inactivated vaccine, because it wouldn't need to be but would be consistent with what the recommendations would be generally for currently circulating viruses.

CHAIRMAN DAUM: Very interesting potential consideration as to what this committee's discussion would look like in a live attenuated vaccine era. Thank you very much, Dr. Patriarca, for your usual crystallizing and focusing comments. And we'll move on now to hear from Dr. Murphy.

DR. PATRIARCA: Well, actually --

CHAIRMAN DAUM: Oh, I'm sorry.

DR. PATRIARCA: -- yeah, Dr. Midthun wanted to briefly go over the questions.

CHAIRMAN DAUM: Would you please do that?

DR. PATRIARCA: Just so everyone will keep these in mind as the presentations go forward.

CHAIRMAN DAUM: My mistake.

DR. PATRIARCA: And I'm hoping that AV guys realize that this is going to happen or supposed to happen.

CHAIRMAN DAUM: That will quickly be apparent.

DR. PATRIARCA: Okay, so, let's see, we're still 15 minutes behind. Sorry about that.

CHAIRMAN DAUM: That's okay. It was very helpful.

DR. PATRIARCA: I actually don't have -- maybe I could start reading the questions until the slides come up. I don't have a -- okay. So what I'd like to do is just briefly go over the questions. These have been, right, Nancy, distributed as part of the package that's available to everyone, is that correct, including the people in the audience? Is that correct? Okay.

We're going to have two questions for the committee tomorrow and we're also going to have two discussion points. Oops, here we go. Okay, the first question pertains to efficacy; "Are the data adequate to support efficacy of FluMist™ in pediatric and adolescent populations, that is to say 1 to 17 years of age? If so, please discuss the appropriate schedule, i.e., one dose versus two doses. If two doses are recommended, please discuss the age range for this regiment and the recommended timing of the doses. That is to say the interval between doses".

And then secondly, "The adult population defined here as age 18 to 64. In your discussion, please address the adequacy of the challenge data submitted in support of efficacy against H1N1". As you will hear later on this afternoon, there is no clinical data pertaining to the efficacy of H1N1 and so, you'll be hearing about some challenge data later today.

"If the data are not adequate for specific age ranges, please discuss what additional data should be requested". The second question pertains to safety. "Are the data adequate to support the safety of FluMist™ in the population in which an indication is being sought, namely 1 through 64 years of age? Please discuss the adequacy of the data in subjects less than two years of age in the overall pediatric population, in adolescents and in adults, specifically adults greater than age 50. If the data are not adequate for specific age ranges, please discuss what additional data should be requested".

The third item is a discussion point not a voting point. "Please discuss the need for data on concurrent immunizations, for example, in children and in travelers". And then finally the fourth point, "Please discuss any additional concerns and/or data

that should be requested; for example, use of this vaccine in high-risk subjects; secondly, annual re-vaccination in adults; thirdly, the assessment of attenuation; fourthly, the potential for transmission or reversion of vaccine strains and then finally, the potential for reassortment of vaccine strains with wild-type influenza viruses".

CHAIRMAN DAUM: Now we'll say thank you and ask Dr. Brian Murphy if NIH to provide us with an overview of development of cold-adapted, live attenuated influenza vaccines, the basis for attenuation, potential for reassortment with wild-type viruses in nature. Welcome, Dr. Murphy.

DR. MURPHY: Can you hear me? Is this on? Can you turn this on? Okay, there we go. I want to thank Peter for asking me to come and speak today. I've worked on live attenuated influenza virus vaccines from 1970 through 1955 -- up through 1995. I hope the rest of the talk is clearer than that particular statement. And it's based on this experience and a lot of personal experience with the cold-adapted viruses that I'm talking today.

My current position is, I'm the Co-chief of the Laboratory of Infectious Diseases at NIH and we are -- we're working on other vaccines currently.

Now, this talk is going to be in three parts. The first part is about a five-minute overview of the salient points of the biochemistry and biology and epidemiology of influenza viruses. The second is I'm going to talk about the cold-adapted viruses and the third part of the talk is to address the concerns of what are the potential for rassortment of the cold-adapted virus genes with wild-type viruses, what are the potential complications of such interactions.

So to start off with the introduction of the biology of this virus. Influenza virus has a segmented genome. It codes 10 proteins. There are the polymerase proteins that are involved in transcription and replication. Hemagglutinin protein is responsible for a binding infusion. The NA protein is responsible for -- probably for a little bit of penetration but clearly for release. This is part of the transcription complex and is a structural protein.

The M1 is a membrane protein, structural protein. The M2 is also a structural protein. It's the ion channel that's required for successful penetration and initiation of infection. NS1 is an interferon antagonist. NS2 also known as the NEP or nuclear export protein, is a structural protein that's involved in getting the influenza virus replication

complex out of the nucleus and into the plasma membrane where these viruses undergo assembly.

Okay, the major property, one of the reasons we're here today, is that this virus undergoes genetic reassortment and two viruses infect a cell, it replicates and then viruses bud and they can have genes from either parent. This is the genetic basis of the generation of the new pandemic influenza viruses. It's also the genetic basis for the techniques that's used to make the live attenuated virus vaccines. The influenza viruses are acute infections of man. They grow to a pretty high titer. We've seen titers as high as 10^7, in the nasopharyngeal specimen as it comes down and antibody response, but the important thing is it's an acute infection. It doesn't stay around very long and after day 10 to day 15, the virus is really gone from the body in contrast to herpes and HIV which have a long lasting association with humans.

Now, this is really a crucial slide because based on a tremendous amount of work that's been done, that quantitates the amount of virus replication and the illness that's associated with that. You can make a curve that shows that the amount of virus replication, high levels of virus

replication, and here if you can't see this, this level of virus replication is 10^6. People who have this amount of virus will have high fever, signs of lower and upper respiratory tract illness.

Okay, this is very important. The sickest I've ever been in my life is when I had the Hong Kong flu in 1969. I was normal at 10:00 o'clock in the morning, had a 105 fever that evening. I would have had this amount of virus present in my nasopharynx. Now, very importantly for the live virus vaccine is the fact that low levels of virus replication are associated with attenuation. You can nicely infect individuals without the occurrence of significant infections. As you'll see, the cold-adapted virus we're talking about and all the reassortants generated from it replicate in this range.

Wild-type viruses generally have a pattern of replication like this. The cold-adapted vaccine in seronegative children replicates around three lives, up to around 10 days of replication. The vaccine in seronegative adults replicates to a lower peak titer and for a shorter duration, indicating the effect of immunity, even if these volunteers are selected for lack if antibody to the hemagglutinin and they'll still have a decreased level of replication. The CA

vaccine in the elderly, this particular set of patterns of replication to some extent dictate how these vaccines can be most efficiently used, very highly immunigentic, much more so than inactivated vaccine in the seronegative child. In the elderly they'll definitely have a role, I'll discuss that subsequently, in seronegative. It also grows in seropositive adults and immunized seropositive adults. We'll talk about some of the results of efficacy later.

Now, the virus undergoes two types of antigenic changes, antigenic shifts, antigenic drifts. The antigenic shift is simply picking up a novel hemagglutinin gene from the population of birds, generally and it becomes substituted for the current influenza virus strain. Antigenic drift is just a change in various antigenic sites that dot the hemagglutinin and generally two or three of these sites are changed every two or three years. That's why you have the need to update the vaccine.

The influenza vaccine takes advantage of the -- of this ability to undergo gene reassortment, make two viruses and you isolate what we call the 6:2 reassortant. All the genes from the attenuated donor virus, the new altered either antigenic shifted or

antigenic drifted glycoproteins from the drift virus. Now, the immunity to influenza virus is basically pretty straightforward. It's generally antibody-mediated. Resistance to infections antibody-mediated. Antibodies that are -- the virus stays pretty much confined to the epithelial cells of the respiratory tract. Antibodies have to be operative in the tracheal and lumer of respiratory tract and the role of the antibodies is to prevent infection, try and keep down the number of cells that are infected. Antibodies that diffuse from the serum or those that are produced locally either IgG or IgA participate in this resistance.

Extensive studies that look at it have clearly demonstrated the role for protective antibody, a protective role for antibodies directed at the HA serum, both IgA and IgG nasal washes can independently contribute to resistance NA as well, clearly a role for serum antibodies, much less is known about this. The importance of this is that this very complicated two antigen nature of protective immunity, multiple compartments, multiple isotypes within compartments, it's almost impossible to predict by doing a simple serologic assay what factor is going to be associated with immunity.

Now, what I'd like to do now is to talk about the cold-adapted virus, major concepts underlying the development of this cold-adapted A or B virus. And what I'm going to be talking about is the demonstration of the transfer of the six internal segments from the cold-adaptive virus to each new epidemic virus confirms the properties of cold-adaptation, temperature sensitivity and attenuation of genotypes, that this specifies a satisfactory level of attenuation in humans and it provides the efficacy that is necessary.

I believe that this -- that the amount of information that exists, the extensive study that is done with this indicates that there's enough information that's available to preclude much testing on an annual basis and that what we're really looking at is whether the licensure for this should very seriously consider licensing the process, not just the vaccines that are ultimately made.

Now, the derivation of the cold-adapted Ann Arbor, the A component, this was done by Dr. John Maassab and he passed the viruses at gradually lower temperatures in primary kidney (phonetic) and derived a virus, cloned it, and by passage at 25 degrees and isolated a donor virus. This passage history about 30

passages in PCK, an it is shown to have a ts phenotype, a ca phenotype and an attenuation phenotype in ferrets. This virus has been sequenced and compared to the sequence of the Ann Arbor 6/60 donor virus. There's one mutation in the PB2 gene, four mutations in PB 1, three in PA, several in NP, one in the M2 gene and one in the MS1. These are the genes that are thought to be associated with attenuation of this virus.

I'll provide more information on the three polymerase proteins and at least the M2 protein as well. Now, the ts phenotype of the Ann Arbor A, HAH2 donor virus, these are the phenotypes. If you look at the level of replication of -- level of replication at 25 degrees, the CA virus grows very efficiently at 25 degrees, wild-type virus don't. Thirty-three degrees both viruses grow well. The CA virus is restricted in its replication at 39 degrees. This is the temperature sensitive phenotype.

The B donor virus was derived in pretty much a very similar way, passing it, lower temperatures deriving a virus at the ts/ca and attenuation phenotypes. This virus has been sequenced. There were an enormous number of differences between the CA and the wild-type virus

from which it was derived. So then they just compared what were the differences of the sequence of the B, the cold-adapted virus from other -- all the other wild-type B viruses that were analyzed at the time and it has a similar pattern of sequence changes.

This is the gene, only gene, that's unequivocally been identified to be associated with attenuation as far as I know at this point in time. Almost certainly these other genes are involved as well. This virus has a very similar spectrum of phenotypes as the Ann Arbor donor virus. It is -- the wild-type virus is restricted replication at 25 degrees. The CA virus replicates efficiently at 25 degrees, again replicating at 33, highly restricted replication of this at the -- at a restrictive temperature.

Now, here is some of the data from ferrets, just to give you an idea. Here's the wild-type virus. Here's the CA derivative of this. It grows very nicely in the nasal turbinates, it's definitely less than the wild-type but still there, highly restricted in the lungs. The B/Texas wild-type virus, again, replicating very nicely in the nasal turbinates, growing in the lower respiratory tract. Here was have the CS donor virus containing the six

genes from the cold-adaptive virus, glycoproteins from this, very restrictive in replication in the lungs and replicates about 10^{100} fold less in the upper respiratory tract.

Now the B virus has also been studied in hamsters and chimpanzees. The virus is highly restrictive in replication of the lower respiratory tract of chimpanzees. This is the B/Ann Arbor. This is a reassortant virus. This is very important. People are always concerned about what will these viruses do in the lower respiratory tract of humans, et cetera. The people have not done pulmonary lavages on individuals who have been administered the live attenuated virus vaccines, but we put both the Influenza A and the Influenza B reassortant into chimpanzees and the replication to lower respiratory tract of chimpanzees is very restricted and it's just -- it's very restricted, almost not recoverable on most of the days that were sampled.

This is the level of attenuation of the B/Ann Arbor virus. Oh, I think I actually -- this is a mistake. This should be that A/Ann Arbor/6/60 viruses. It's basically identical. The level of replications of the -- okay, I don't have the data on the -- I don't have the data on the ferret data with

the A/Ann Arbor/6/60 viruses but it's identical to that what I've showed you for the B/Ann Arbor virus.

What I want to do now is review with you the properties of the CA reassortants in humans and the properties that have been systematically examined over a very prolonged period of time with the level of attenuation, its infectivity for humans, genetic stability, transmissibility, and efficacy. Efficacy's been studied in individuals of different ages. We're talking now mostly about monovalent vaccines. None of the studies I'm going to be talking about are studies that are the formulation of the trivalent vaccine that you're considering.

Attenuation, the summary of the results, these are highly attenuated for seronegative and seropositive individuals, you need 10^7 viruses to be infectious. The ts and ca phenotypes are very stable. The virus is poorly transmissible. It's very immunogenic in infants and young children, much more so than the inactivated vaccine. Young adults, live and activated vaccines look alike. Elderly, the live is weakly antigenic but the live plus the activated is more efficacious and I'll show you some data suggesting that.

Now, this is how we did the -- how we

looked at these viruses. We did challenge studies in adults who were selected for seronegativity to the hemagglutinin present in the cold-adapted virus. You might not be able to see this but we looked at two influenza H3N2, two viruses and two influenza H1N1. We looked at the wild-type virus which is this bar or the CA virus and this is the percent of the systemic illness and I think you can see in each case we were very nicely able to reduce the illness that's associated with wild-type influenza viruses by generating reassortants that contain the six transferrable genes from the A/Ann Arbor/6/60 donor virus.

Level of replications are very similar to what I've described earlier. Each of the wild type viruses grow four or five logs, the live attenuated, mean peak titer in seronegative adults around 1 to 2 logs. Okay, this is really the basis of attenuation of these viruses. They replicate less well in the respiratory tract of humans. Similar analysis has been done for the B/Ann Arbor CA reassortment viruses. The -- we looked at the mean peak titer replication in adults and children but the variety of the B/Texas virus, the B/Ann Arbor/60, A virus or the B/Yamagato (phonetic), these are all 6:2 B reassortants. In each

case the wild-type virus was replicated much more efficiently in the upper respiratory tract of adults and the wild-type viruses were not put in children but these levels of replication of the viruses of the cold-adapted viruses, cold-adapted B viruses that have been evaluated in children have been to the same levels of those that we've seen with the cold-adaptive influenza A virus, same levels of replication.

Now, what are the genes of this virus that are associated with attenuation? The way we went about and the way this has been studied by others is you take a wild-type virus, you mate it with your cold-adapted donor virus and then you isolate reassortants. We isolated reassortants that derived one gene from this virus, from the donor virus and the contacts of wild-type genes from the -- and this way you could describe the phenotypes of this virus to the gene derived from your cold-adapted virus. We did this, we actually made volunteer pools up of each one of these -- each one of these preparations, put them in humans and did very careful comparisons with the wild-type virus to try and get an idea of which of the genes are associated with attenuation.

From this analysis, first of all we were interested in determining which of the genes were

associated with ts and ca phenotypes. And this actually -- this actually -- we got a very clean reading based on this. The cold-adapted phenotype is specified by a single gene, a PA gene. We will see subsequently that this also an attenuating gene. The ts phenotype is independently specified by the PB2 gene and the PB1 gene. Okay, so this is the genetic basis of two phenotypes which are associated with the attenuation phenotype.

Now, these six single gene reassortments were also looked at for their level of replication in ferrets, hamsters and humans. The level of replication in ferrets and hamsters of the two viruses bearing the ts mutations were clearly significantly restricted here. We had a difficult time testing for significant restriction in humans but these were both lower in their level of replication. P18 was clearly attenuated as a single gene in both the ferrets and humans. And then the M gene was attenuated in ferrets and humans. I think that this virus has a -- at least four genes that are associated with attenuation in humans, the three polymerase proteins and the N proteins.

We also had the opportunity to investigate in humans a reassortment that just had this gene and

this gene. It was a non-temperature sensitive virus but it is just as attenuated as the six gene reassortant virus. I think this virus has redundant mechanisms of attenuation that are conferred by the -- this set of ts genes and then non-ts mutations. I think this is very important because the high level of genetic stability that's exhibited by this virus. I don't think we've ever seen a revertant in testing this over a very long period of time attests to the fact that it has multiple genes contributing to attenuation. When you test a virus that's just temperature sensitive, it reverts very readily.

It's the combination of the ts and then the non-ts mutations that contributes to the high level of genetic stability of this particular virus. And this is true for other viruses that have been evaluated in this way. I don't think we'll -- this just gives you a schematic look at -- you take the NR donor virus and you look at what -- these are the mutations that are present in the PB2 gene, the PB1 gene and the PA gene and the attenuations. I also have the M gene on this. It has mutation at M2, so there are at least four independent mutations on different genes that contribute to the attenuation phenotype for humans.

Which of these mutations or whether more than one or two contribute to the attenuation phenotype, which of these contribute to the CA phenotype remains to be determined. Now, the property of infectivity, what's known about that, infectivity, you simply take a influenza virus, you dilute it out and you test the frequency of infection looking at either the shedding a virus or the antibody response. You determine this. You determine a human infectious dose 50 and you look at the large set of data that's been derived doing this for both the Ann Arbor/6 -- the H1N1 virus, the H3N2 and this, of course, is the A group we're looking at here.

In adults, the mean infectious dose 50 is around $10^{3.5/5.7}$. When you give 10^7 of this virus which is generally the amount of virus that's given in the vaccines, you're giving approximately 10^{100} human infectious dose 50 of the virus. The infectious dose 50 in children is a little bit less and therefore 10^7 of the virus is -- represents around 100 to 500 human infectious dose 50's. The same type of information exists for B CA reassortments, the adults, the human infectious dose 50. Two studies have been done 55, 65, which is around 10^6. In children it's around $10^{3.5}$.

Safety and level of virus replication, I've talked about the level of virus replication data on genetic stability. There are various ways of determining genetic stability. One is you can determine the genetic basis of attenuation. I've described some efforts to do that which has been pretty successful for the sub-group A viruses. You can identify surrogate markets of attenuation, the ts phenotype and ca phenotype. This has been done and this is predominantly the method that's been used to look for the viruses and characterize the viruses that have come out of infected vaccinees.

Let me just go back here. Excuse me for a second. You can also do other things. If a vaccine actually has an altered phenotype, you can take that virus out, do some clonal analysis of it and do a variety of things to determine whether the phenotype is associated with -- has been altered following replication. I can tell you right now that all the work that's been done and we did a lot of this, and this is actually -- this particular virus was a competitor for viruses that I was working on at the time and I'm doing all these studies with this particular virus and I've never seen an unequivocal loss of the ts and ca phenotype that went to wild-type

level and any virus that has shown an alteration in its level of temperature sensitivity, when it was put back into the ferret, it maintained -- this study was done by John Maassab, it always maintained the attenuation phenotype.

So there's never been a situation where the virus that's been given to a human has been carefully analyzed, the virus coming out that's been associated with the loss of attenuation phenotype, I believe that's the result of the fact that it has four genes independently contributing to this particular phenotype.

The genetic stability, many studies have been done, as I say the ca and the ts phenotype is maintained in the majority of these. This has been looked at for both H3N2, H1N1 viruses. It's actually been done in a large number of viruses, even more than looked at here. A similar type of analysis has been done for the 6:2 reassortants of the B/Ann Arbor/6/60 virus. These are the reassortants and these are the numbers of isolates that have been looked at or original nasopharyngeal washes that have been characterized. And again, a large number show the maintenance of the property of the ts and ca phenotypes.

Since there was less information really available on the B/Texas virus, we did a study where we took the B/Ann Arbor 184 CA virus, put it into immune suppressed hamsters, isolated a virus that we got 15 days later and we made -- from six different animals and we put it back into hamsters. I was working very hard to see if we could get revertants to do this particular study and the viruses that -- and we evaluated the passaged virus versus the unpassaged virus in the nasal turbinates and lungs of hamsters. Wild-type virus grew well. Attenuated unpassaged CA donor virus was restricted, as we've seen. All of the viruses, despite extensive replication, showed and maintained the attenuation phenotype. Again, it really gave a lot of -- it gave us a lot of assurance that this virus was -- this particular virus was highly stable.

The conclusions on genetic stability, we think that these viruses are both phenotypically stable and that this is not a major problem, lack of genetic stability. We don't think this will be a major problem. Now, there have been a large number of studies that have been done, and these studies were generally done by Peter Wright. He had three or four vaccinees, a susceptible placebo, all housed together

in a little playroom setting and he looked at the ability of the viruses to spread from the vaccinees to the contacts. In all of those studies we never saw the -- and these are the number of infected vaccinees. These are the number of contacts. We never saw the virus transmit to the contacts.

That does not -- and the importance of this is several fold. First of all, these are seronegative vaccinees. They're growing the virus, they're growing the virus to the highest level. They're growing the virus at $10^{3.5}$, the virus is not transmitting. We were very interested in why. The reason I think it's not transmitting is of you know the human infectious dose 50 for this virus, for these particular seronegative contacts, you need around, as we saw, about four, five logs approximately $10^{4.5}$ logs of virus to infect 50 percent of them. These volunteer generally shed around three logs. So we think that they're shedding less than the human infectious dose 50. That's one.

These vaccinees rarely have symptoms, so they're not showing -- we think these two factors add up to a very poor and low level of transmissibility of this particular vaccine for humans.

Efficacy, there have been efficacy where

monovalent vaccines have been studied extensively in adult wild-type challenges, pediatric subjects and then been studied also in seronegative individuals and also seropositive individuals. And I'm not going to go through the extensive data on this. I just wanted to indicate that these are studies that have been done with challenges of H1N1 viruses and H3N2 viruses in adult volunteers screened for susceptibility. The wild-type virus is generally, as you saw earlier, made these volunteer sick. Attenuated viruses infected them. When they were challenged, I think you can see there's a high level of protection against systemic illness in the volunteers. Also, this was associated with clear and unequivocal restriction of virus application in the vaccinees, decreased number and decreased quantity of virus, the decreased number of challenged individuals infected with the wild-type, decreased number of -- decreased quantity of virus shedding.

The same type of thing occurs if you challenged seronegative individuals, not with the wild-type virus but with the attenuated virus. You see a high level of protection and you see protection after a very long period of time. Short periods of time, you have a high -- a year later you maintain at

least 54 percent of the individuals are still resistant to replication of the challenge virus.

I'm just showing this. I know that the Aviron will discuss this, their efficacy trial. The important point I want to make here is, is that this efficacy that they're seeing in this natural infection is very similar to what was saw in all of these challenge studies that we've done in experimental settings and not in the natural setting. The importance of that is, is that there are multiple times when we've demonstrated efficacy against H1N1 viruses.

I know there is some limited data with H1N1 viruses natural settings but we've seen it every time that we've looked for it in our challenge studies. Now, here's another very interesting point and these are studies that were done by John Taeanor, three separate challenges, three separate studies that were done where they compared the efficacy in this case, against natural infection with the monovalent cold-adapted H3N2 Influenza A virus and he compared an activated group versus an activated live. And this was the efficacy that was in addition to that conferred by the inactivated vaccine.

And I think what we saw in this case, that

there was approximately -- you can measure an efficacy of 65 -- 60 percent approximately. That's above and beyond, this is in elderly individuals above and beyond the protection that was afforded by the inactivated vaccine. This was a very important lesson because what it taught was that there was certainly room for improvement of the activated vaccines. Everybody who's used them, knows that's the case.

This documents a way to improve that efficacy. Although you're not considering using this -- the indication for the licensure is not for people who are older, this really indicates that the live attenuated virus vaccines will be able to supplement the efficacy of the inactivated vaccines. And we think the reason that it does this to -- first of all the activated vaccine is much more efficient in introducing serum antibodies than the live.

The live, in contrast, is better in stimulating local antibody. The sum of these two positive properties is responsible for this higher level of efficacy that is seen. Okay. Now, these are the properties we've talked about. These are the number of reassortant vaccines that we studied or studied as a part of the whole NIAID, including the intramural, extramural branches. These are the number

evaluated for safety and the properties were demonstrated.

The important thing here were that there were seven or eight other vaccines that were developed during this period of time and each one of them fell off. Some of them were not safe. They produced a febrile illness or too much -- most of them were satisfactorily infectious. Some -- most of them -- most of the problems really were safety or genetic stability. The virus with just ts mutations were not genetically stable. The viruses that were -- we had problems with avian and human reassortants of -- viruses H3N2 viruses not being very satisfactorily attenuated, even in kids, but H1N1 viruses were not.

So this set of properties -- the cold-adapted virus is like the energizer bunny. It just kept going through each one of these things and doing extremely well and it went through every one of these tests and survived whereas all of the other vaccines that we tried fell off this pathway. And that's all I wanted to say except just summarizing the possible uses. Live virus vaccines will be very useful in seronegative individuals. In the individuals who are between the young infants and children the elderly the live virus vaccine and the inactivated vaccine both

work and they're good. I think a lot of people would much rather have something put in their nose than a shot in their arm.

The elderly, I think that you're going to -- if you want to get optimum protection in this age group, you're going to have to give both. They both give you different -- stimulates different parts of the immune system. Those are just some thoughts for you to consider.

Now, I want to just address in the last five or six slides some of the problems that are associated with one of the issues regarding the introduction of the cold-adapted virus into the general population, what does this mean for a generation of reassortant viruses and what does it mean for the issues regarding unknown generation of reassortant viruses. Now to do that, I'm just going to review briefly some of the properties of the pandemic influenza virus since 1918.

We had one in 1918, 1957 and 1968. These viruses have been very carefully characterized. In 1957 when the H2N2 virus came along, it picked up PB1 NA from an avian virus. The reason I'm pointing this out right now is the cold-adapted virus is derived from this particular virus. In 1968, the new virus

picked up a new -- the H3N2 virus picked up a new hemagglutinin and kept the neuraminidase, picked up a new PB1. The other virus -- this virus is circulating today. The H1N1 virus was very similar to a strain that existed in 1950 -- the H1N1 virus present around 1950 appeared back in the population in 1970. These two viruses circulate today.

We'll revisit some of the issues regarding this. What are the other examples of the introduction of animal or avian influenza viruses into the human population? The H1N1 virus is from swine -- you all remember the swine flu. That got into the human population and caused some problems. The H1N1 virus from birds seems to have gotten into pigs, reassorted with pigs, generated a virus and picked up an H3N2 code, got back into humans. This is documented in 1993. H7N7 avian virus is from pet ducks, gotten into the humans and have caused infections.

H5N1, we know all about the avian bird flu from 1997. H9N2, from market birds in 1999. There's been a lot of introduction of genes, much more different from the genes that are present in the cold-adapted viruses. The humans are constantly being probed by these viruses to see if they can -- just to see if the viruses can take off. What happens is --

what's happened in these cases -- okay, this is just some of the specific examples. The H1N1 swine flu is a introduction of the swine virus. This is some type of reassortment with some avian genes and some human genes, got into the human population.

The H7N7 virus from birds, H5 from birds, H9, these are really problems -- humans are going to have problems with genes from avian viruses. They're going to come from wild-type viruses. They're going to come from viruses in the circuit. They're not going to come from out cold-adapted virus and I'll give you the reasons why I believe that. The consequences of these viruses, as you know, the 1918, '57 and '68 viruses are severe pandemic viruses. The swine virus caused severe infections in humans but did not cause a pandemic. Okay, this was also true of the H5N1 virus, severe infections in individuals, abortive infections in humans.

The H1N1 virus became epidemic. The H7, again, was abortive, only seen in one individual. Now, the -- the third source of these influenza genes come from laboratory studies or experimental studies. I think many people believe the H1 virus was a 1957 strain, somebody was working with it. It got into a laboratory worker, got into the population. That's

one scenario that's reasonable, makes sense based on the information that exists.

H7N7, avian virus that was present in seals, got into a human, it caused conjunctivitis. The direct inoculation, people have been administering various avian viruses to humans from time to time for the purpose of making experimental vaccines. Now, what is known now about the interaction of viruses. The current trivalent vaccine will have an H3N2 and an H1N1 component. What's known about the mixture of genes from H1N1 and H3N2 virus is what has been circulating in the population together since 1957 -- 1977.

The various combinations have been documented by investigators and you can get reassortments. These reassortments can be -- contain H1N1 virus, all the other genes from H3N2, various mixtures. In fact, there are a lot of mixtures that have been identified. You can find a variety of H1N1's, antigenic mixtures, et cetera. The important point of this is that first of all these infections, these transfer of genes between H1N1 viruses and H3N2 viruses are going to continue as long as these viruses circulate between wild-type viruses.

Okay. The important point is, is that

these viruses that were identified, they cause transient circulations of the viruses in the population. These viruses will not persist. They will always be replaced by the H1N1 or H3N2 parent viruses. They do not seem to be a strong selective pressure on them. They seem to just sort of cause a little epidemic here or there and then were replaced by the other viruses. The illnesses that were seen in individuals from whom these viruses were isolated were identical to the -- either the H3N2 or H1N1 wild-type virus.

Okay, I've just got one or two more slides. Okay, so what that meant is, is that there are probably no significant consequences of mixing the H1N1 and H3N2 viruses and this will occur in the vaccinees. I would imagine almost very vaccinee that you give an H3N3 and H1N1 component vaccine together will generate reassortant viruses.

They all share the same six internal genes so that can undergo a significant exchange. Now, one of the consequences of introduction of genes present in the ca virus into the human population, but can these genes -- are there any threat of getting the internal genes into the population and what are the consequences, possible consequences of reassortant of

genes present in the cold-adaptive virus with those present in animal or avian viruses?

Okay, now just to review again, the 1960 -- - the vaccine virus, the ca donor virus was derived from this H3N2 virus. It contains genes related to the H1N1 virus as does both the H3N2 and H1N1, currently circulating H1N1 virus. We think there are no -- you know, these are just different versions of the same gene, the same is true of the PA and the PB2 except that these genes all have attenuating mutations or most of them have attenuating mutations.

Only the PB1 gene differs from the currently circulating virus. Okay, this is actually -- - the ca reassortant viruses have this gene. The currently circulating viruses have different PB1's. So this is the only sort of novel gene, but this is not really a novel gene. It is 97 percent related by amino acid sequence to the genes that are present in the H1N1 or the H3N2 virus. So when you look at this, the high degree of genetic relatedness of the internal genes that are present in the ca donor virus, we not think that there should be any problem of those particular genes getting into the population, the same problem of those genes getting into the population shared by the wild-type viruses.

Now, this is the main -- are there unique consequences of reassortant between genes bearing new HA or NA genes from avian or animal viruses and one or more genes from the ca. What's the chance of the ca virus picking up novel HA's or NA's and how does this differ from the wild-type virus? We think that it will be very -- okay, I'll just -- we think it will be very unlikely for this to be a significant problem. The ca virus is poorly transmissible. It's almost certainly not going to get into an animal virus or a bird enabling it to undergo a combination in that host. Therefore, there is certain -- it will likely occur in humans.

The ca virus is present in lower titer and for a shorter duration in vaccinees and this would decrease the opportunity with which a reassortant could occur. At least 50 percent or even more than that of any kind of reassortant virus between a ca virus and the wild-type avian or animal virus will have ca reassortant genes.

This is my last slide. This is actually a lot of -- there's a lot of information in here. The ca vaccine at the time of the possible pandemic, if you have a ca virus vaccine available at the time of a pandemic vaccine, you'll be very lucky. Generally,

it's very difficult to isolate a new pandemic virus, make a reassortant, generate clinical lots and do studies. So we think that this is really not an issue. It's certainly not an issue for inter-pandemic influenza viruses.

Clearly, you would not -- okay, now if a -- if you did, if you were very wise and had made a whole variety of ca reassortant viruses bearing H4, H5, H6 genes and had them all ready at the time a new virus appears, you have a new virus in Asia, wants to come to the United States. Should you be able to introduce that virus because it could undergo the combination with the H1N1 circulating viruses in the United States at the time and generate a wild-type virus. The answer is, yes, you would probably go ahead and use it when the certainty of a pandemic virus arriving in the United States is 100 percent.

In the case of an abortive infection, you would never use this virus, okay? You would never use this virus and introduce it into the population where there are -- a virus bearing novel glycoproteins, ca donor viruses into an open population where wild-type viruses are circulating unless that virus -- unless the virus was -- unless the virus was a pandemic virus. Abortive infections that occurred in 1977 and

the swine -- and the swine flu or the bird flu, you would not use a cold-adaptive virus vaccine bearing those glycoproteins unless those viruses became pandemic.

So I don't think that people would use these viruses or consider using them at a time of a pandemic -- I think you would -- I don't think that they'll be available for the time of the pandemic in the next 10 years but if it were available, you would use them to prevent the spread but you would never use them and introduce them into a population to -- in a situation where you have an abortive epidemic.

That's it.

CHAIRMAN DAUM: Thank you very kindly, Dr. Murphy. I hate to not provide the committee an opportunity to ask a couple questions that might be clarified regarding your presentation. Are there a few questions from committee? Ms. Fisher, Dr. Myers, Dr. Schild.

MS. FISHER: If up to 20 percent of the population every year get the flu, I believe that's the estimate, up to 20 percent of all people get the flu every year, what are the potential long term epidemiological consequences of targeting every baby, child and adult for exposure to these flu viruses

albeit an attenuated form? In other words, have you looked at the potential for mutation of the viruses into vaccine resistant forms leaving a majority of the population without true immulogoical memory and more vulnerable to future possibly more virulent flu pandemics and has there been any assessment or evaluation of the long term immunological integrity and overall health of those who are vaccinated every year with these live viruses versus those who are not?

DR. MURPHY: I think that's an extremely complicated question. The important relevant experience is the experience that has been gained with a lot of live virus vaccines that have been utilized to date and generally the information from using these virus vaccines has been that the consequences of the infection fall within the range of what you'd expect with a wild-type virus except that they're highly attenuated compared to the wild-type virus. So that you can -- if there are specific problems associated with the wild-type virus in terms of altered immunological consequences, you might see those with these live attenuated viruses but they would always be much, much less frequent because the virus is going 1,000 fold less well, et cetera.

The -- although 20 percent of the

population develops illness, a lot more become infected. A lot of the population becomes infected with these viruses, has illnesses that don't bring them into the physician with wild-type viruses. We don't think that there should be anything different about these live attenuated, cold-adapted virus vaccines used as an immunogen, versus what occurs with the wild-type virus. The wild-type virus infects a large percentage of the kids on an annual -- more than 20 percent.

CHAIRMAN DAUM: Three more crisp question askers and crisp answers. Dr. Myers, please.

DR. MYERS: Would you build on your last comment and tell us about concern or your thoughts about the use of cold-adapted vaccine in travelers to, for example, Asia, and then just something that I wasn't clear from what you said is does productive chick embryo productive infection imply virulence for flocks?

DR. MURPHY: Say that once again.

DR. MYERS: Yeah, does the enhanced productive infection that occurs in eggs imply a virulence for flocks?

DR. MURPHY: No. I mean, these viruses are -- would basically be apathogenic for a livestock,

bird, et cetera. Human virus is really -- you could -- you can't find hardly any information or literature about human viruses going into livestock and associated with lots of problems. There's some H3N2 viruses that have been in pigs, et cetera, but if these viruses can to into livestock the wild-type viruses will be there, okay, before these cold-adapted viruses would ever be there.

And your first question was?

DR. MYERS: Using the vaccine for travelers to Asia for example.

DR. MURPHY: Well, I don't think that would be a problem. I mean, there shouldn't be any inherent problems of using this vaccine in travelers. I think the concerns that were raised about their compatibility with other vaccines would be an issue, a separate issue, but in terms of generating reassortant viruses, you have to remember that the H3N2 and H1N1 viruses are widely distributed throughout the world, okay, so that, you know, they're there. There won't be anything unique occurring, any specific problems associated with the cold-adapted vaccine.

DR. MYERS: I was trying to ask the question about the point that you were making at the

end about never utilizing in the setting of --

DR. MURPHY: Let me --

DR. MYERS: --circulating other strains.

DR. MURPHY: Right, let me clarify that point. The ca recombinants, you would not use them, you would not make a ca recombinant virus and introduce it into the human population in the setting of two -- in the settings we know about. You would not have done that back in 1977 when the swine flu virus came along because it caused an abortive epidemic. You would not have done this when the H5N1 virus came from birds to pigs. You would not make an H5N1 cold-adapted virus and introduce it into the population.

You would only use the cold-adapted virus during novel glycoprotein genes and the threat of a bona fide pandemic virus and you'd have to have a very special group of individuals who would say, yes, this is a bona fide epidemic. That's what I was trying to make -- that point I was trying to make.

CHAIRMAN DAUM: Thank you. Dr. Schild, then Dr. Griffin.

DR. SCHILD: Very masterly review of a very complex subject. I believe the reappearance after 25 years of an H1N1 virus that continues to

spread in co-donors is still an enigma that requires and explanation in relationship to what we do when we work influenza viruses. Have you any reasonable hypothesis explaining how it hid for 25 years and --

DR. MURPHY: Well, I think it was -- I mean, I would say -- this is a little bit off the topic, but I think the virus, somebody was working with it on the bench top, somebody who was not immune to H1N1, got it in their nose, went home, brought it home to their kids and the epidemic started from that, in that way. That to me, makes the most sense.

And I would share with you, and as Peter had indicated on the slide, working with viruses such as the H2N2 virus, everybody who has been born after 1968, okay, you be very careful and reassortants with this virus have to be done under -- where you can generate an H2N2 wild-type virus. So if you're working with an H2N2 wild-type virus, I think that you have to show considerable caution in that and maybe learn from the H1N1 experience. But I don't think that has anything to do with using the cold-adapted virus in an open population.

CHAIRMAN DAUM: Dr. Griffin?

DR. GRIFFIN: My understanding of your data comparing both replication and infectivity in

adults versus children was that, first of all, it's more infectious for children than it is for adults and second of all, it replicates better and by a log approximately for each of those two. So question number 1 is what were the ages of the children that those graphs were generally taken from? Were those one year olds, or four year olds or eight year olds?

DR. MURPHY: No, no, no, the seronegative kids are all -- would generally be between six months and 36 months of age.

DR. GRIFFIN: Okay, then the second question was, what do we know about those same parameters, infectivity and replication, in immuno compromised -- I know you won't have any data on immuno compromised children probably, but in immuno compromised animals, I don't know, ferrets or hamsters? You had a little data on prolonged replication, but --

DR. MURPHY: We just did that one experiment with hamster with the B donor virus. I have not looked at the prolonged replication of these viruses in humans. The interesting thing about --

DR. GRIFFIN: And level --

DR. MURPHY: The interesting thing about influenza viruses in general is, is that individuals

with AIDS, et cetera, they don't stand out or influenza -- or in people who are undergoing bone marrow transplant. They don't stand out as the major problems in those settings. RSV, PRV are the major problems in those settings indicating that there is not a lot of information out there that would suggest that influenza viruses in general or these viruses in particular would be especially problematic in immuno suppressed individuals, such as AIDS who have partial immuno suppression.

Does that answer your questions, Diane?

DR. GRIFFIN: Well, I have a more elaborate -- but yeah, that gives an approximate answer.

CHAIRMAN DAUM: Thank you very much, Dr. Murphy. And given that it's not an airplane day for committee members, I think we'll take a lunch break. It's 12:35 here in the Eastern Time Zone and we'll reconvene at 1:35, one hour from now. Thank you.

(Whereupon, at 12:35 p.m., a luncheon recess was taken.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:39 p.m.)

CHAIRMAN DAUM: Good afternoon. Welcome back from lunch. The FDA staff outside the room has been kind enough to take messages for people that need to be reached here within the conference room. You might want to check out there with the staff if you're expecting something. We're looking for a Dr. Dominick who people apparently are trying to find and have left a message out there from this morning. I'm sorry, Dominick Iacuzio, thank you, Dr. Bleshe.

We move to the afternoon's agenda now which are presentations from the sponsor and from the FDA. Dr. Greenberg will begin the presentation and -- I did good -- and what we're going to do is to have the first two sponsor's presentations and have committee input after the second one. We will -- the sponsor's presentation, I'm told is 90 minutes long and we will not charge them the time for the committee discussion. So those are the ground rules that have been negotiated and so we'll have two presentations in a row and then committee discussion and then the other three, with committee discussion in between. Without further ado, Dr. Greenberg.

DR. GREENBERG: Thank you, Mr. Chairman,

members of the committee. I'd like to make a brief remark before I go on and that is that this morning you heard that there are ongoing discussions between the FDA and Aviron from Dr. Patriarca and this is true and they are highly collegial and ongoing and we expect them to continue in the future and we're very appreciative of the FDA for interacting with us.

So this afternoon you're going to hear about the clinical spectrum with FluMist™, the influenza vaccine for use in healthy children and adults, ages 1 to 64. The proposed indications for this vaccine are annual immunization for prevention of influenza in healthy children 1 to 17 years of age; two doses one month apart for previously unvaccinated children less than 9 years of age and one dose for previously vaccinated children and children greater than 9 years of age, for healthy adults, 18 to 64, one dose.

Not proposed for use in high risk children and adults, people with a history of allergy to chicken eggs, children or adolescents receiving aspirin, women who are pregnant or people concurrently being vaccinated. Well, you've had a very brief discussion of why we're looking at vaccines for influenza and I actually mentioned this previously,

but I want to bring home the message again, and that is that influenza is an equal opportunity package and by that I mean, it effects all age spectrum of the population, from our very youngest children to our elderly and it takes a big toll across the population.

So this is data from Dr. Glezen, who may or may not be in the audience, I haven't seen him but I thought he would be here but I could have taken it from any number of people, indicating, as you heard that in the area of mortality the effect is really greatest in our elderly. Hospitalizations, however, a type of morbidity occurs both in our elderly and in our young, children under 5 being most effected and then medically attended illness, illness that probably took Dr. Murphy to a doctor back then when he got the pandemic flu, really occurs across the population with its greatest effect on our young people.

There are limitations with the current influenza vaccine program. There are 150 million healthy people currently not vaccinated. Vaccination rates in healthy children are less than 10 percent despite this very big burden of disease. Vaccination rates in healthy adults are less than 30 percent. The need, current need, already outstrips supply and an annual injection is required currently and the vaccine

that is currently given is not delivered at a mucosal surface where virus replicates.

Next slide. So the vaccine that we're talking about and you've heard this from both Dr. Levandowski and from Dr. Murphy, is a live virus that contains that hemagglutinin and neuraminidase gene segment of the current epidemic influenza viruses and the remaining segments from the attenuated Master Donor Strain. It's manufactured in specific pathogen-free eggs. There's no preservative in the vaccine, no thimersol and it's stored frozen. It's trivalent containing 10^7 tissue culture infectious doses of each of the strains in a half an mL and it's administered by a nasal sprayer as a large particle mist, 60 micron in average diameter and it's a quarter of an mL per nostril.

Well, you've all gotten vaccinated and I won't belabor you with showing you what a shot looks like, but you've heard some talk about nasal sprayers and I think it would be good for you to see what vaccine administration by a nasal sprayer is. So this is a young girl being administered a dose of FluMist™. As you can see FluMist™ administration is easy and well tolerated. Next slide, please.

You also heard about the substantial

history of the investigation of this vaccine and I wanted to bring home this message, so this vaccine, live influenza vaccine milestones over the first three decades and I've given you for a reference point the presidents who were in office during that period of time. John Maassab, who has been sick and unfortunately cannot be here today but he was the inventor of this vaccine -- the first published cold-adaptation back in 1967. Actually, I was just leaving college at this time.

The first human studies carried out with 6:2 reassortants that you've heard about were in 1976, over 25 years ago. There were lots of studies and I've only put on one here, the four -- it's actually five years, but four years of data because of wild-type circulation, the Vanderbilt Study was one of the big studies showing this vaccine, a bivalent formulation and how it worked and how safe it was and that was in the late '80's. And Aviron entered the picture in 1995.

By 1995 and that's when you're going to start hearing the story after I get off the podium, 19 separate influenza strains in over 8,000 people had been tested and generally, they were shown to be safe and effective. Next slide, please.

There are however, I just want to bring home to you some differences between the studies you're about to hear about and that historical record that is being covered. The studies that are going to be described this afternoon are all carried out with trivalent composition vaccines. The vaccines have been annually updated to as best as could be predicted, meet what was circulating in the community. That's not always possible, as you'll see. Consistent doses have been given to children and adults. A consistent 6:2 genotype has been used in all of these studies and the vaccine is administered by large particle mist. In most of the previous studies it was administered by nasal drops.

And finally, the data that you're going to see presented are really relatively large clinical trials and much of the historical record is smaller clinical trials. Next slide, please. So the way we're going to do this now is, you're going to first hear about safety and you're going to hear about a large scale safety trial carried out in Northern California Kaiser by Dr. Steve Black and that will be followed directly by safety in children by Dr. Paul Mendelman which will join all the other safety in children with the Kaiser study. I want to remind you

and the point with these safety studies is that the safety of this vaccine should be discernible to you in this very large safety data base that we're going to present in over 9,000 -- in over 18,000 healthy children, and in this Kaiser study, in over 9,000 total enrollees.

Following the discussion of safety in children, we'll have safety in adults. Then we'll move onto efficacy and effectiveness in adults and that will be given by Dr. Kristin Nichol from the University of Minnesota and the Minneapolis VA; then efficacy and effectiveness in children, Dr. Robert Belshe from St. Louis University medical center and I will give some brief concluding remarks. Thank you. Dr. Black.

DR. BLACK: Good afternoon. I have the privilege now of describing to you a clinical trial that we had the opportunity to conduct in our population to evaluate the safety of the Aviron FluMist™ vaccine through medical utilization in t he clinic emergency room and hospital to assess possible occurrence of rare adverse events. The first slide, please.

This study was a randomized, double blind, placebo controlled clinical trial and employed a two

to one randomization with twice as many children receiving the FluMist™ vaccine as placebo and occurred at essentially all of the sites within Northern California Kaiser Permanente. The dosage scheme that we employed was similar to what was just described for two doses for healthy children 1 to 8 years of age, given at least one month apart and a single dose for healthy children 9 to 17 years of age.

Next slide, please. The primary objective of this study was to evaluate the safety of FluMist™ in this large cohort of children by comparing within a 42-day observation window following receipt of either FluMist™ or placebo the rates of medically attendant adverse events, in other words, clinic visits, hospitalizations, or what we'll call ED visits or emergency room visits, the rates of those events for all observed diagnosis, that is without a priori hypothesis as well as for pre-specified group diagnoses that we'll talk about a little bit later.

We're also comparing the occurrence of serious adverse events in the two groups as well. Next slide, please. The analysis format, I think, as you'll see, is this -- as we present this, but it's important to bear in mind employs a lot of different comparisons being made. We analyzed the data by site

of care, emergency, clinic, hospital or anywhere combined analysis by dose, Dose 1 or Dose 2 or regardless of dose and by as you can see, multiple age groups and for each diagnosis that was observed in each one of these analysis.

Overall, there are more than 1,500 different comparisons being made without statistical adjustment for the multiplicity of comparisons here and that has implications that I'll elude to as we go on. Next slide, please. This gives you an idea of the enrollment in the study. There are 9,689 participants, again, to remind you of the two to one randomization. Here there was slightly more children in the younger age group by design than in the older age group.

Next slide, please. What I'm reporting on today is an interim analysis that was done as of data that was complete through the end of last year. The study began in the fall of last year and by the end of December of 2000 enrollment was complete. All participants had received one dose and 88 percent of the total Dose 1 follow-up time was complete. Sixty-four percent of second doses had been administered and 43 percent of Dose 2 follow-up was complete as of the data that I'll be presenting. And overall, 72 percent

of the total follow-up time was complete.

Next slide, please. To give you an idea, these are all of the diagnoses that we did observe in the study. So there really are a lot of different diagnostic comparisons that were being made. Next slide, please. And another way of giving you an idea of the lay of the landscape here overall is that you can see that .4 percent of FluMist™ participants and .4 percent of placebo participants experienced a hospitalization during the 42-day window. ED visits, as you might expect, were more common, at about two percent and clinic visits and children during the winter season as all pediatricians in the audience will know, are quite a common event but there's 28 percent in each case.

Next slide, please. These are the four pre-specified diagnostic groups that were analyzed; acute respiratory tract events, systemic bacterial infections, acute GI tract events and rare -- potentially rare events that have been -- that are known to be potentially related to influenza infection and to summarize these results here, there is no significant risk difference in the rates between the two groups. This shows the rate per 1,000 person months and this is the relatively risk and P-value.

Next slide, please. When we look at the diagnostic categories where we did not pre-specify the outcomes, this table summarizes the results that were observed and I should comment this is using a one-sided test and a P-value of .1 for significance, so it's quite conservative in terms of trying to identify events that might be associated with vaccination. There are, as you can see here, roughly an equal number of categories of events that have decreased relative risks that are significant and those that have an increased relative risk and we're going to focus on the left-hand side of this chart for a moment and especially on the first four events where we felt, based upon what we knew about the way the vaccine was administered and influenza that these had biologic plausibility although we'll address all of these as you'll see.

Next slide, please. Now, in order to look at these further based upon the initial analysis, we did several things. We did -- looked at the time course of these events, what was the time relationship between receipt of vaccine and the onset of the events. We would anticipate for any physiologic phenomenon that there is some defined time interval between vaccination and onset. We also looked at

review of prior history which included determining whether the onset of the even pre-dated receipt of vaccine.

We did descriptive review of individual cases from medical records to try and characterize the event and finally, for two of the outcomes where we were trying to characterize them further, we did parental interviews to determine the nature and character of these events for abdominal pain and conjunctivitis.

Next slide, please. The first of these outcomes we're going to talk about is conjunctivitis. We observed 96 events in 90 patients. The incidents, as you can see here, was relatively uncommon with 1.1 of FluMist™ participants, .7 percent in placebo. However, we did observe this in multiple utilization settings, multiple age group analysis and multiple dose comparisons and the fact that we observed these in multiple comparisons to out mind makes us think of them as it would be more likely to be a real phenomenon. So these are the settings where we observed them and these are descriptive factors that we obtained in talking to the parents and reviewing the chart. That was a concomitant diagnosis in about two-thirds of the children in both groups and prior

history in about 12 to 19 percent.

Eye discharge appeared to be more common in the placebo group than in the FluMist™ participants and pain was quite uncommon in either group. Next slide. This gives you an idea of the range of the relative risk that we did observe and as you can see, these range roughly between 1.6 and almost 3 fold increase in relative risk but remember the incidents is still relatively uncommon. You can see this occurred in both the youngest children and the middle aged children, if you will, and then the overall age group as well.

Next slide, please. This graph -- let me orient you to this because we'll be looking at more of these. This shows the number of FluMist™ participants on this side and the number of placebo participants on this side and the scale is different to try and correct for the fact as you look for this visual aide that there are twice as many FluMist™ participants as there are placebo. And in looking at this, we see that there's a clustering of these conjunctivitis events toward the beginning of the observation window. Again, our interpretation would be giving this higher physiologic plausibility.

Next slide, please. So in summary, we saw

a temporal association with vaccination. These were mild and self-limited, I should say, in review of the medical records. There was no specialty referral or any sequelae observed at all and the attributable risk depending on the setting that you look at, is somewhere between 2.8 and 11.6 cases per thousand person months. So our conclusion, our interpretation is that there was an apparent low level increased risk of conjunctivitis with receipt of FluMist™ vaccine.

Next slide, please. Another outcome that we observed at increased risk as asthma. Asthma was -- a history of asthma, according to the parent, was an exclusion criteria from participating in the trial. Nonetheless, we observed that asthma was observed in the combined setting only for this age group only, following Dose 1 only, a very different situation than what we observed for the conjunctivitis. There were six cases in the FluMist™ group, zero in the placebo group and the P-value here is .04.

Next slide. If we'd look at the time course of these events, you can see they range from 12 to 41 days, so there isn't really any consistent time relationship. Next slide, please. And of these six patients with asthma, four actually had a prior history, prior to participating in the trial, two had

had a history of many URIs but no prior asthma diagnosis and the onset of these two children were at the two extremes of the time window that I talked to you about.

So our interpretation here is that the lack of a consistent temporal relationship suggests that the increased relative risk for asthma in these young children was not related to vaccination. Next slide. Another outcome we observed was otitis medial with effusion. It was also observed with increased risk. For the non-clinicians in the audience and not to insult the clinicians, otitis media with effusion is not the same as what we normally call an ear infection. The children, although it can be associated with ear pain, but is more of a chronic inflammatory process associated with fluid and is a chronic condition.

We observed this to be elevated in the clinic setting in the young children 1 to 8 years old and only after the second dose of vaccine with a 21 to 4 case point estimate for the relative risk of 2.6 and a P-value of .03. Next slide, please. If we look at the time course of events here, you can see that this is quite spread out. However, we feel you'd need to interpret this with -- somewhat with caution, since

this is a chronic condition and the date of onset, really is difficult to determine.

Next slide, please. But in summarizing this, we did not observe a consistent temporal association. Medical record review revealed a prior diagnosis of otitis media with effusion in three-quarters of these children roughly, whether they were in the FluMist™ or in the placebo group, so the majority these children had this prior to receipt of vaccine. So the nature of a relationship, if any, between otitis media with effusion visits that we saw and FluMist™ following Dose 2 really we cannot determine from these data.

Abdominal pain was also observed in one analysis to be elevated and the emergency department only in 1 to 17 year old children for combined doses. You can see the case split here is 11 to 1 and the ratio is 5-1/2 which is statistically significant. So we evaluated this further again by looking at these graphs which you're probably now tired of looking at, but again, there's no consistent time association here at all, not clustering toward the vaccine or further away. It's completely spread out.

Next slide, please. And of the 11 cases and the FluMist™ recipients, specific etiology was

subsequently assigned in 4 and actually confirmed in 2. One child had pneumonia with a positive x-ray. One child had a urinary tract infection with at positive urine culture. The diagnosis in one child was felt to be pain secondary to ovulation due to the timing and localization and character of the pain and one was felt to be due to stress in the family, due to what was going on in the family and that child was referred to psychiatry.

Next slide. Additionally, if we look at abdominal pain in other settings, the clinic or combined settings, we actually see statistically significantly decreased risks of abdominal pain occurring with ratios here, as you can see varying between .33 and 4 in the clinic or combined setting in 1 to 8 year olds. Next slide, please. And if we look at all settings after all doses combined, all settings could include hospitalizations but there weren't any. You can see here again that there's no statistically significant -- there's no evidence of any association between abdominal pain and receipt of FluMist™ vaccine.

Next slide. If we look further, since we know that abdominal pain has been something that's been of interest to the committee recently, we look

further at other events that might be associated with abdominal pain including, as you can see here, appendicitis, gastroenteritis, and rare events which include intestinal obstruction and intussusception. There was one -- in the data that I'm reporting to you here, there was one case of appendicitis in a child in the FluMist™ group, zero in the control group. This is slightly different than what's in the briefing book because we've had an opportunity now to include the pathology data which confirmed this child was actually having appendicitis and another child actually which was included as appendicitis is having negative pathology.

That's this child here and really for the other events, there was no data that would support any level for concern, vis-a-vis, these events. Next slide, please. So in summary for abdominal pain, in this study we saw no consistent clinical presentation or temporal relationship to vaccine. When we interviewed the parents some of the pain was diffuse, some was dull, some was sharp, some of the pain disappeared between when the child registered in the emergency room and by the time they were seen it was gone. Some of it lasted for days longer. There was no consistent localization.

There was no evidence of an association with potentially serious consequences. The relative risks were inconsistent as I pointed out to you. However, as Dr. Mendelman will mention in the talk that follows me, there was an increased risk of abdominal pain as ascertained through parental diaries observed in another study. So we feel that the lack of consistent clinical presentation or temporal relationship observed in this study again suggests that abdominal pain observed in the emergency department was unrelated to FluMist™.

Next slide. These are the other outcomes that we observed with increase risk and let me just point out a couple things. One of them, speech delay was observed. However, six of the seven children observed with this had speech delay identified prior to participation in the trial. Enuresis, similarly again, all these children had this prior to the trial. Benign lesion and cellulitis were observed. These were a lot of contributing diagnoses and no consistent body site. And the cellulitis was, again, all over the map in location in terms of where this was as well.

Next slide, please. I'd like to make the committee aware, we've had an opportunity -- what I've

reported to you on here is this analysis through December. We've had an opportunity now to look over the last week at the final data set and I'd like to highlight the differences which are quite few, between the final data set and what we observed in the interim analysis. Overall, the results are really quite consistent. There were two diagnostic categories that were observed with an increased relative risk, elective procedures and warts, neither one of which caused us much concern because we didn't feel that there really is any possible physiologic mechanism for this. And two, medically attended adverse events that were previously observed with an increase relative risk were no longer statistically significant, benign lesion and cellulitis, which as I pointed out, we were not very concerned about before that anyway.

And to highlight the influence of multiple comparisons here there were eight new diagnostic categories with decreased relative risk were identified. Next slide. So overall we concluded that FluMist™ in this large cohort appear to be well tolerated. There was no increased risk in the FluMist™ recipients for any of the pre-identified diagnostic groups. Serious adverse events occurred at a low rate in both groups and in blind did an

evaluation by the investigators. None were felt to be vaccine related.

Several outcomes observed with elevated risk and biologic plausibility were evaluated further, as I've highlighted to you here. Abdominal pain was not consistently observed or associated with serious sequelae. Muscle aches and ear or eye symptoms, although we highlight them, were observed but had been reported in prior studies and are known to be associated with vaccine. And conjunctivitis we felt was associated with receipt of vaccination and although the risk is low.

And finally, several biologically plausible outcomes had reduced risk, including interestingly acute GI tract events, cough, febrile illness, tonsillitis, viral syndrome, wheezing and shortness of breath. Thank you very much.

CHAIRMAN DAUM: Thank you, Steve. We'll move right onto Dr. Mendelman's presentation and then have some committee discussion.

DR. MENDELMAN: Good afternoon. My name is Paul Mendelman. I'm Vice President of Clinical Research at Aviron. I'm honored to be here and I'd like to thank the FDA and the committee and legion of individuals for their individual efforts and their

collective efforts over the past 25 years to bring this day to fruition. And I'd particularly like to thank Dr. Maassab and the National Institute of Health. One housekeeping issue is that in order to stay within time and keep it off of our clock, some of the slides you got yesterday I'm not going to present but I'll take questions.

The first slide presents the data from '99 peer review journal articles prior to the Aviron experience. In those articles, the 6:2 reassortant cold-adapted vaccine were studied in over 8,000 individuals and 2,743 of these individuals were children. These were primarily monovalent or bivalent formulations and these vaccines were found to be safe and well tolerated. The next slide presents the Aviron experience; 18,390 healthy children which includes the vaccinees in the Kaiser trial that you just heard about from Dr. Black, in 1 to 8 year olds, 12,069 in the 9 to 17 year olds, 6,321 children. There were high risk populations that were studied and the total is 1,317. So the overall number of children dosed with FluMist™ is 19,707.

The next slide shows the collection of safety data in the various trials. The methods included a symptom diary card. This was completed by

the parent or guardian in the children trials, the monitoring of medical records by the contract research organizations and co-monitoring with Aviron personnel, telephone calls from the investigators, the investigators' staff to the participants' parents or guardians as well as health maintenance organization data base review.

The types of events included serious adverse events. In children these were collected from day zero to day 42 and also post-vaccination reactogenicity events which in some early studies were day zero to 7 and in later studies were day zero to 10. These were events that might be expected to be observed with viral replication or with wild-type influenza and a parent or guardian had to check a box, was it present or was it absent or did it exist. And these were pre-specified events, nine events, which I'll go over with you shortly as well as temperature documentation with a thermometer on each of those days.

The parent also reported on the diary card any event that occurred within that post-vaccination period that was not pre-specified. And they also recorded the medication use that was taken during that time interval. The next slide presents the

demographic characteristics for the children 1 to 17 years of age broken by the younger age group 1 to 8 and the older age group, 9 to 17. On average the younger age group was 4 year of age and the older age group was 12 years of age. There was a balance in gender between the two age groups and there was a balance in race ethnicity and the race ethnicity was similar to the general U.S. population overall.

The next slide presents the serious adverse events in the clinical trials by age and population. In the healthy children 1 to 8 the incidents rate was .4 percent; in the placebo recipients it was .5 percent; in the healthy 9 to 17 year olds, .3 percent in the FluMist™ recipients and .1 percent in the placebo recipients. In general the serious adverse events were low and nearly all of these were considered by the investigator and reviewed by Aviron as being not vaccine related. I will present in a subsequent slide the vaccine related serious adverse events that have been observed to date.

The next slide presents the mortality in children in these over 19,000 children that have been dosed. There was one death due to bronchopneumonia 27 days after the second dose. This child was in a trial

conducted in South Africa by Wyeth Lederle vaccines. This child on the diary card, after the first dose, had no temperature recording on a digital thermometer that was recorded as febrile on each of those 10 days and the child did not have any other reactogenicity events which were systematically recorded. They were all noted as not present by the parent.

Six weeks later the child got the second dose and again the child remained afebrile after the second dose, all 10 days of the recording, and had no events other than a runny nose on day zero and day 3. Unfortunately, approximately 24 days after the dose, the second dose, the child had an episode of vomiting, sought medical care, got penicillin for a couple of days and had a rapid respiratory death, very soon after hospitalization.

The other death was a child with a brain tumor and complication of malignant hyperthermia, 145 days after dosing in a second season. This was also not considered vaccine related. The next slide presents the vaccine related serious adverse events. There were two in vaccinees. This was in a study in children initially enrolled at 12 to 15 months of age. A child came in what wheezing six days following the second dose. The investigator felt it was medically

important and therefore, was serious. And another child 14 months of age with bronchiolitis 21 days following the second dose. We've had a third vaccine related serious adverse event that we were told about yesterday after you got your briefing document slides.

This child was also in this study, was 16 months of age. The child had gastroenteritis and croup 10 days after receipt of the second dose and was hospitalized overnight. There actually were two vaccine related serious adverse events prior to unblinding. The investigators determined this and then subsequent unblinding they were noted to be placebo recipients. One was a case of laryngitis in an 18-month old three days following the first dose and the other was a case of croup four days following the first dose in a 21-month old child.

The next slide presents the review of the systematically collected reactogenicity events following the first dose and this varies somewhat from your briefing document that we provided in that in the briefing document we provided all children integrated, regardless of whether they were placebo controlled trials or not and in the data I will go through with you here these are in placebo controlled trials so we can provide statistical analysis on which events were

statistically significant in a correct statistical fashion.

This slide shows after Dose 1 the nine events that were systematically collected as well as temperature and what is observed that runny nose, nasal congestion is higher in the FluMist™ recipients than in the placebo recipients. Muscle aches was also increased and the low grade temperature of an oral temperature of 100 degrees Fahrenheit was increased statistically over the placebo recipients looking at a temperature of 102 there was no difference statistically between the two treatment groups.

The one event, just to highlight to you here, vomiting, is our GI event or gastrointestinal event within the reactogenicity period and you can see there's no difference looking at all the placebo controlled trials and that may be seen somewhat as a surrogate for abdominal pain. The next slide presents the by day of occurrence analysis for the temperature analysis. And there's a peak on day 2 and there's a statistical significant increase on day 2 and day 3 in the FluMist™ recipients compared to the placebo recipients.

The next slide presents the data after dose 2 in the same season and for all of the events,