ahead of you if we're going to move on. So you're second.

But any other issues with transmissibility? Fair warning, although we can return to it if someone needs to.

Dr. Markovitz.

DR. MARKOVITZ: Yes. I wanted to follow up on a question Dr. Myers posed earlier, which I thought was very appropriate, and I think we need to hear a little bit more about, and that has to do with just how reactogenic the allantoic flu and placebo was, and I'm wondering whether there are some data comparing this to a true placebo because obviously the vehicle for the vaccine does count in terms of how patients perceive what's going on.

And I'm wondering. From the tables it's kind of hard to tell when it says, for example, that a patient had a runny nose or whatever. I mean, was this the runny nose to end all runny noses or was this a little runny nose?

In other words, is this something that would have patients coming back and saying, "I'll never get that vaccine again," or is it just one of those little things?"

And I don't know that I've heard any

data to speak to this issue.

CHAIRMAN DAUM: Let's reframe that or frame that by are there data comparing reactogenicity with other placebos? I think that's fair.

DR. MARKOVITZ: I think Ed Connor started to answer that before, in fact, but I'm not sure I fully followed it. So --

CHAIRMAN DAUM: Let's hear from Bob Belshe and then Ed Connor and if there's other data bearing on this issue, let's hear them next.

DR. BELSHE: Hi. I'm Bob Belshe from St. Louis University, and I've been involved in a number of these clinical trials.

The data we're displaying here is a clinical trial of a different intranasal vaccine. These are the saline placebo recipients in young children age six to 18 months. Now, they selected at time zero on day zero for the absence of illness. Specifically, they do not have a cough. They do not have a runny nose.

And you can see at the end of day one 12 percent have a runny nose. They're receiving saline intranasally.

And so what we believe this phenomenon

represents is selecting a healthy population who normally have about 20 percent of the group having rhinorrhea or runny nose, and so this is a return to the mean by day five to seven. We've returned to the mean where about 20 to 25 percent of children here have a runny nose.

And so this is, I think, a very good example, which is a true saline placebo and not normal allantoic fluid and reflects what we've seen in the FluMist trials.

CHAIRMAN DAUM: Bob, that's very helpful data.

Dr. Connor, did you want to expand on that?

I have Dr. Snider next.

DR. SNIDER: Well, I was going to change the topic unless you wanted to stay on it.

CHAIRMAN DAUM: No, I think we've addressed the question, and we can move on to the topic of choice.

DR. SNIDER: Okay. The topic of my choice at the moment has to do with the efficacy data and particularly the fact that we're being asked to make some comments about the adequacy of data to support the efficacy of FluMist in

individuals five to 17 years of age and 50 to 64 years of age.

And as has been mentioned earlier, although there is quite a bit of safety data available for the five to 17 year age group, there is at least not in the BLA data with regard to efficacy.

And then as has been pointed out by FDA and others, the number of people in the 50 to 64 age group is considerably less than in some of the younger adult groups.

And I was wondering if the sponsor could make some comments about why that was the case, what the problems were in trying to get numbers of people there in those age groups or if there is historical information they feel, you know, has an important bearing on this issue, if they could tell us what that is.

CHAIRMAN DAUM: Thank you very much, Dixie.

Is there a sponsor response?

DR. CONNOR: I think there weren't any particular difficulties in getting patients into the study. The studies were simply done as childhood studies that went up to 71 months of age and as

adult studies that included patients all the way up through 64 years of age.

Our view, I think, is that we've clearly been able to demonstrate efficacy in children, and we've been able to demonstrate effectiveness in adults, and that there doesn't seem to be a biologically plausible reason why the middle group would have any other different effect.

The studies were simply designed and executed in the way that they were looking at specific issues in children and adults.

The issue of the 50 to 64 year olds is a post hoc fact, that is, that's how many patients were in the trial as the trial was recruited, and I think that our view of looking at that data is that, first of all, when you look at all of the specific or the more specific influenza measures within the AV009 trial, you see reductions in measures of effectiveness.

In addition to that, when you actually look at the days of illness, clearly there weren't differences when you look at the group as a subset among the occurrence of illnesses, except in the DOD ILI definition, but across all of the other measures of effectiveness for severity of illness, days of

illness, day of missed work and antibiotics, you see significant effects in all of those measures.

So I think the perspective is that we've demonstrated efficacy in children. We've demonstrated effectiveness in adults. The issues about any of the age groups go to the question of whether there's any evidence that there were differences in the populations either of children and adults in that population, and we actually have seen no substantive evidence that there's any difference.

Certainly in the pediatric population the data that we showed suggests that there is not even a trend to anything happening as you get to the edges of the population base, and the data that we've shown in the 50 and 64 year olds, while smaller in that population, doesn't have significant evidence that that population is substantively different than the population as a whole.

There weren't any other issues or difficulties related to actual inclusion of those other populations.

DR. SNIDER: So if I understand correctly, you're saying from a biological standpoint you feel like we should be able to

extrapolate to the five to 17 year old group based on the other data.

And then as far as the 50 year olds and older, I guess I was wondering. I mean it may have just come out that way depending on who was served by the particular caregivers who participated in the trial, but I was also wondering if maybe people were excluded because there were at that age a lot more people who wind up with contraindications, and that may have been a reason why they were smaller.

DR. CONNOR: Maybe I can ask Kristin Nichol, who conducted the effectiveness trials to make some comments.

DR. NICHOL: Kristin Nichol from the VA Medical Center, Minneapolis, University of Minnesota, one of the investigators for AV009.

Dixie, with regard to the specific question about enrollment, there were no specific difficulties of which I'm aware, and of course, we conducted AV009. This predated the ACIP recommendations putting people 50 to 64 in a high priority group because about 25 to 30 percent of them are high risk.

By the way, the ACIP is not suggesting that healthy people 50 to 64 are high risk. They

are high priority because about a quarter to a third of them may have a high risk condition.

So there were no specific issues. We certainly did exclude participants who had any of the ACIP indications for vaccination at the time that we conducted the trial.

With regard to the question about evidence of benefit or lack thereof, perhaps I could make a comment as well. Again, the 50 to 64 year old high priority designation from the ACIP came after this trial. So this is truly a post hoc analysis.

We did pre-specify an analysis by age 40, under and over 40, and did not find any evidence of a differential effect. With regard to the 50 and over, there are fewer subjects, only about 640. So we do have limited power to have precision in our estimates or to find significant P values.

However, as summarized in this slide, which looked at the febrile upper respiratory illness category, you will see that the confidence intervals for people 50 to 64 around the point estimates for effectiveness across the different outcomes categories include the point estimate for the entire group, as well as the point estimates for

people 18 to 49.

There is imprecision in those estimates, particularly in occurrence in days of illness, somewhat amazingly actually given the sample size. We do find statistically significant benefit when we look at days of work lost, health care provider visits, and antibiotic use.

If we looked at other health care illness definitions, you would see a virtually identical pattern.

But in any event, we are not able to see any evidence of a differential effect by age.

CHAIRMAN DAUM: Thank you very kindly for those comments.

Dr. Myers, please, and then Dr. Gellin.

DR. MYERS: Well, I had a comment and then a question.

The comment, Ms. Fisher, is that between 20 and 25,000 Americans die every year from influenza, and so it is a significant disease, and although we don't see the damage from polio as a consequence of influenza, it is disease of significant morbidity and mortality, and I just wanted to correct the record on that.

My question for the sponsors, I was

really glad to see the HIV data because that helped a lot as we're struggling with these questions. With that said, the absence of data on high risk patients is really striking from your application, influenza being a disease with specific high risk groups.

And the reason, and I was wonder if there's other data. That's my question. The concern, of course, is that as a licensed vaccine is utilized, we've already seen the asthmatic in the children, but they're going to be high risk people immunized inadvertently either accidentally by transmission or more commonly because they just don't know their high risk because they have underlying diseases.

And so I was wondering if I could ask the question about the absence of the data, your plans to collect that data or what your thoughts are about inadvertent administration of vaccine to people who have high risk conditions.

CHAIRMAN DAUM: So that's a very worthwhile question. We'll ask Dr. Mendelman to respond, and I'd also like to hear from Dr. Mink on this question as well.

DR. MENDELMAN: The question is broad,

and prior to formerly Aviron pursuing the studies or initiating the studies with FluMist, there were 99 peer reviewed journal articles in the literature and 32 review articles, and that went back about 25 years, and in those studies, they were published, and I'm sure there were file drawered studies that were not that we're aware of also, children with cystic fibrosis were studied; children with bronchopulmonary dysplasia were studied; children with asthma were studied.

Now, these are small numbers, Dr. Myers, going back, but when you add them all up, they come up to that number of 8,091 that was shown on one of the initial slides by Dr. Young across those 25 years of studies.

Now, studies in chronic obstructive pulmonary disease were also, you know, conducted as well so that there's a supportive data base that goes back 25 years, but the data that the FDA has to review on our file are there that we've submitted to the agency.

And so there's a background of supportive information that, you know, one could give credit to because they are the Maassab master donor viruses that were made in those monovalent and

bivalent.

And if I could have that first slide, George.

The largest study, of course, is Dr. Edwards' study, and the question has been brought up about repetitive -- it's in the new slide set, George -- and it was conducted over five years. It's one of the largest or largest studies between 1985 and 1990, 5,210 participants, one to 64, and most of them were over 15 years of age.

And in that study, and the design is shown here, there were -- of the four seasons when flu circulated, two were H1N1 seasons and two were H3N2 seasons, and the next slide will show the data for all participants, and you can see that this was compared to inactivated vaccine; that in 1986, 1987, that the cold adapted bivalent, 78 percent with confidence intervals you see, and the inactivated vaccine, 79 percent. That's with the H1N1, and 1988, 1989, 90 percent, point estimate for cold adapted and 74 percent for the inactivated.

And then in the two H3N2 years, 59 percent and 56 percent for cold adapted and 71 percent and 79 percent for the inactivated.

And in the publication Dr. Edwards notes

there was no serious reaction to the vaccine across these five years of study.

Subsequent to that, in the next slide, Dr. Neusel (phonetic) pulled out the pediatric data with Dr. Edwards from that trial. There were about 800 children in that trial who received a bivalent cold adapted, and you see here the efficacy similar for both the inactivated vaccine and the bivalent vaccine in that trial by Dr. Edwards of Vanderbilt.

CHAIRMAN DAUM: On this very subject and very brief.

DR. CONNOR: I just wanted to as Brian Murphy again if he wanted to comment at all on the high risk populations that have been studied previously.

DR. MURPHY: No.

DR. CONNOR: Okay. That's fine.

CHAIRMAN DAUM: Thank you very much.

Dr. Mink, could you speak for the agency on this issue?

DR. MINK: What we consider as part of the BLA is the product is manufactured by the sponsor with the clinical safety data submitted in support of the labeling indication requested. So what we consider in reviewing this product are the

20 studies that have been reviewed and presented to you.

CHAIRMAN DAUM: I guess if I could press you just a little bit, if there were a licensure of such a product is there a position yet or is it too early to ask as to what would be required afterwards in terms of assessing these issues?

That's what I really --

DR. MINK: That's discussion point number four.

CHAIRMAN DAUM: You will hear from us.

(Laughter.)

Dr. Edwards, this very issue?

DR. EDWARDS: Yes.

CHAIRMAN DAUM: Okay.

DR. EDWARDS: I have a question, particularly in the 50 to 64 age group. Why the approach was taken to not do an efficacy trial or given the fact that there is a licensed product that now is suggested to be given in that age group, why there might not have been studies that compared the licensed and the unlicensed product.

I think effectiveness measures are generally not what we see for licensure.

CHAIRMAN DAUM: Sponsor want to speak or

FDA want to speak to that question? It's a good one.

DR. NICHOL: I guess I'm the elected official, or unofficial person.

CHAIRMAN DAUM: Thank you.

DR. NICHOL: With regard to effectiveness versus efficacy, it's my understanding that this was discussed at some length before the onset of the trial with various people. I'm looking to the sponsor here, but I'm quite sure there were some discussions with FDA and others with regard to whether or not effectiveness might be an outcome as opposed to culture confirmed efficacy that would be acceptable.

Of course, this is a randomized, double blind, placebo controlled trial. When we looked at effectiveness outcomes rather than efficacy, what this meant for us was several things.

One was that we were interested in looking at a real world outcome, and of course, in the real world most often we do not have culture confirmed influenza that we're looking at. We are looking at people coming into the medical care community with influenza-like illness.

By choosing a less specific outcome than

culture confirmed influenza, which is very specific, we realize that we inflated our sample size need substantially, but we really wanted to have a real world look at what would happen in a population if you immunized them with live attenuated influenza virus vaccine.

Recall, as was discussed earlier today, that when one sees a reduction of, for example, 34 percent in influenza-like illness, if one backtracks to what that might have corresponded to if one had culture confirmed influenza, in a clinical trial of the inactivated vaccine conducted over two years and the second year or actually in the second year of the trial, which was the year after our study was done, the efficacy against culture confirmed influenza, the specific outcome that we're most used to seeing perhaps was 86 percent.

But when they translated that into a reduction in influenza-like illnesses, the kind of clinical effectiveness that we saw, they saw a reduction of 34 percent.

So, yes, we did choose the effectiveness outcome. We were very interested in a real world outcome as opposed to the culture confirmed outcome which doesn't replicate what happens in the health

care provider's office.

DR. EDWARDS: Was there a thought to including in that an inactivated arm?

DR. MINK: At the time that we did AV009, we already had a sample size requirement that was substantial because we were looking at a clinical effectiveness outcome, and we chose not to really inflate the sample size requirement by going to a three arm study.

CHAIRMAN DAUM: Thank you.

I think Dr. Gellin has been patient.

DR. GELLIN: Perhaps a related question, but I'll ask the same question that Kathy had, but maybe inverted and maybe as has been set up as a real world example, maybe this is an un-real world question. So it's a question of the institutional memory that I don't have that other people in this room do.

How often do new products come to a committee like this when the question is efficacy and the data is effectiveness?

CHAIRMAN DAUM: I think we're going to ask for some agency input on that question.

Dr. Midthune.

DR. MIDTHUNE: I can't think of any.

Obviously we have brought products here where the efficacy parameter is the immunogenicity comparison, but those are for products where there have been previous clinical disease endpoint studies.

CHAIRMAN DAUM: Thank you.

Dr. Decker, some industry perspective on this question?

DR. DECKER: Yeah, just a reminder that I think it was the last meeting of this committee we voted or the committee voted to approve a license extension based on effectiveness data, if I remember correctly, Prevnar and otitis media.

That wasn't a totally new product. It was already licensed, but it was an extension of the indication.

DR. MIDTHUNE: That was an extension of that indication, but there were data that actually showed tympanocentesis results where there were actual serotyping of the pneumococcal isolates derived from that.

That was the Finnish study. There was also the Kaiser study, which just looked at acute otitis media, but there was both in that particular application.

CHAIRMAN DAUM: In fact, the issue might

have been viewed quite differently were there only effectiveness data in that instance.

Yes? Did you want to speak to this again? Would you please? Obviously an important issue for us.

DR. NICHOL: Forgive me for coming to the microphone again. Kristin Nichol from Minneapolis, one of the AV009 investigators.

I forgot to mention perhaps, after Kathy's question about effectiveness, just to remind the committee that there is a challenge trial demonstrating efficacy against culture confirmed illness among adults. It's a relatively small trial, but it is an efficacy trial looking at wild type challenge, and efficacy was 85 percent against all three wild type strains combined. The study was not sized to be able to look at efficacy for each type specifically.

CHAIRMAN DAUM: These subjects were 18 to 41 years of age?

DR. NICHOL: That's correct, and they were randomized either to placebo or to receiving the FluMist or trivalent inactivated vaccine.

CHAIRMAN DAUM: Other committee comments?

I guess I would take the initiative then and ask in studies like these or others where we've had efficacy data presented against culture confirmed influenza, do we know anything about the people who failed. Has there been any attempt to study the folks against whom efficacy did not occur? And do we know anything? Is there anything special about them or unique about them that we should hear about?

Anyone want to take that question on? Dr. Mendelman?

DR. MENDELMAN: Again, the proof of principle that we got was the pediatric study, which was culture confirmed and large. The efficacy trial in adults that did involve a TIV arm gave us proof of principle that we could go on and do the large effectiveness trial in adults.

And the supportive data and multiple efficacy trials was submitted in the license application in the historical review section, 7.8, which is certainly available, and that reviews those efficacy trials that were done.

In those, for the committee, and we could present them on screen if you would like, but the range is, you know, wide, but the overall is in

that 70 to 90 percent efficacy for the cold adapted vaccine across multiple efficacy trials, but the largest is Dr. Edwards' that we've noted to the committee, which was comparing it with TIV.

DR. CONNOR: Bob, just to answer your question, I think that the --

CHAIRMAN DAUM: Please.

DR. CONNOR: I think that in most of those trials obviously the efficacy in the pediatric trials were quite high. I mean well above 90 percent, and there obviously were very few of the patients who failed, and we haven't actually characterized those patients any further, but the numbers are really very small also.

CHAIRMAN DAUM: Dr. Katz.

DR. KATZ: This is perhaps to beat a wounded if not a dead horse. That is that antibody studies sometimes help.

(Laughter.)

DR. KATZ: And I was going to ask Nancy Cox because each year when we review new influenza virus vaccines at CDC, she presents us data on antibody response, HAI antibodies usually to new strains, the cross-reactivity with other strains, and you must have some feeling, if not data, not

relating to these studies, but what are the necessary antibody studies and the antibody levels which will guarantee you protection against influenza.

DR. COX: I thought you knew better than to ask that question.

(Laughter.)

DR. COX: There is no specific antibody level that guarantees protection. The level of an HA titer of 40 or greater is often used as an index of protection in the studies that we do and the studies in various vaccine trials. That level is expected to protect about 50 percent of the vaccinated population.

What we can say generally speaking for an activated vaccine is that the greater the antibody level, the better. For live attenuated vaccine, there hasn't been as good a correlation of antibody levels with infection. So there probably are other factors, including local antibody, that are contributing to protection.

But there is definitely some correlation with antibody, even with the live attenuated.

CHAIRMAN DAUM: Thank you, Dr. Cox.

Dr. Belshe, you wished to speak to this

very issue?

DR. BELSHE: Yes. I'd like to just contribute a little bit. Regarding the breakthrough infections in AV006, there were a small number of vaccinated children who did develop natural influenza. Those illnesses were significantly shorter in duration in terms of days of fever, less than two days of fever compared to placebo recipients, which had an average of approximately five days of fever.

So there was a more mild illness in those breakthrough infections.

Regarding the correlates of immune protection, we did extensive studies on behalf of the NIH in the AV011 trial, which was a challenge study using vaccine virus as a challenge. We were able to demonstrate that secretory IgA and serum HAI antibody were independent of correlates of immune protection, and that there was very weak correlation between those two correlates.

So if you had either antibody or secretory IgA, you were significantly protected against a vaccine virus challenge. They were very powerful correlates. Approximately 85 percent were secretory IgA, and more than 90 percent for serum

HAI antibody.

CHAIRMAN DAUM: Thank you, Bob. Those are very helpful comments.

Let me call on Dr. Overturf. I apologize.

DR. OVERTURF: Just as a follow up. In the document that we've all been given, it looks like the historical data on antibody levels shows that the cold adapted vaccine in terms of fourfold immune responses is only about half as good as TIV, maybe 60, 70 percent in some studies.

So that brings up the other issue, and I thought maybe Dr. Cox would address this, is what is used currently standardized each year's lot of vaccine if it's not antibody. Obviously since systemic antibody doesn't seem to be as good with cold adapted inactivated vaccine, what will be used or is that going to be necessary?

DR. COX: I think that that's a question that could best be answered by my FDA colleagues. We're involved in regulatory issues.

CHAIRMAN DAUM: Dr. Levandowski, you want to catch the pass here?

(Laughter.)

DR. LEVANDOWSKI: I'll do my best. The

questions about potency of inactivated vaccines, that's not done by antibody tests using antibodies from animals or from people. It's done by a method that's called single radial immunodiffusion, which is an immunologic type of test, but it's an in vitro test, which is done with a standard antigen, comparison between the standard antigen and the test antigen, which would be the vaccine, and from that the quantity of antigen that's present can be quantitated.

That has been correlated with immunogenicity in studies that were done way back during swine flu and the return to the H1N1 viruses in the late 1970s. So we use the antibody testing in terms of looking at whether current vaccines are likely to make antibody responses that are reasonable to newly circulating strains, but we don't use that so much as a tool to determine whether the vaccine -- let's see -- what the potency of the vaccine is.

I'm not sure I've answered your question.

DR. OVERTURF: Well, the question is: has somebody thought about what will be used as the standard measures for this vaccine, which may not be

the same as used in previous influenza vaccines.

DR. LEVANDOWSKI: Well, now you're asking about potency of this vaccine, I guess is the question.

DR. OVERTURF: Yes.

DR. LEVANDOWSKI: The potency of this vaccine is based on infectious units. So the number of infectious units in the product is what that will be based on.

CHAIRMAN DAUM: Thank you very much.

What I'd like to do is to change gears a little bit now, and we'll take a very short break, but before we do that, we'll put the first question back up on the screen, and when I come back, when we come back, I'd like to have the committee focus on additional issues that need to be explored to deal with the first question.

I think you'll find that most of them have been explored, perhaps not all of them, and then we will begin the process of actually voting and being heard on these questions.

Before we take this break, I'd like to make a brief presentation of my own.

(Laughter.)

CHAIRMAN DAUM: Through the miracle of

Jody Sachs, the committee has been able to procure a present, and the present, of course, is for Dr. Kathy Zoon.

We just learned this morning of your decision to move over to NCI and leave FDA, and it's obvious from Dr. Katz's comments and others' that there are some circumstances here, but I think the most important point is this is an enormous loss for FDA, and I can only hope from what I know of interacting with you all of these years that it's a good move for you and that it will be a wonderful benefit for NCI to get someone of your caliber, but this agency will sorely miss your work.

This is a small token.

(Applause.)

DR. ZOON: I don't want to hold up your break because I know how important breaks are, but I just want to say how much I appreciate your gift. It means a lot to me, and the recognition of both my colleagues around the table, the audience, for your recognition, and in my new job I will try to do my very best to make a significant impact on the public health at NCI.

Thank you.

(Applause.)

CHAIRMAN DAUM: Tax dollars, of course, were not used to fund that gift.

(Laughter.)

CHAIRMAN DAUM: It is 2:35 here in the central time zone -- Eastern time zone. I'm sorry. At exactly ten to three we will reconvene, and with the first question up, we will have question focused discussion.

Thank you.

(Whereupon, the foregoing matter went off the record at 2:40 p.m. and went back on the record at 2:54 p.m.)

CHAIRMAN DAUM: Could the final conversations sort of cease and we move back to our business of the day?

I'd first like to say a special thank you to Dr. Sachs for upgrading the quality of the Musak. I don't know if any of you have noticed, but we've been treated to her tapes and music at lunchtime and during breaks. I must say it's a lot better.

The second thing is as usually happens during these kinds of meetings, there are actually three people who have asked for some time before we turn to the question itself, and so we're going to

hear three separate comments.

First, I'd like to call on Dr. Midthune of FDA to clarify an issue that came up last hour.

DR. MIDTHUNE: I just want to clarify that the sponsor, at that time Aviron, did discuss their plans for the efficacy evaluation with us, and that we were in agreement with their approach to evaluate efficacy for the pediatric population and effectiveness for the adult population.

CHAIRMAN DAUM: Thank you. That certainly helps shed some light on some things people were concerned about.

Dr. Parsonnet wanted to raise a global issue not focused on one question or another, and this is the time to do that.

DR. PARSONNET: I guess my point comes out really from the hat I used to wear, which is on the Anti-infective Advisory Committee of the FDA and where we always had comparators. We always looked at a new antimicrobial agent and compared it to one that was already in existence, and that, I guess, sort of brings up this issue of the elephant in the room here, which is that there already is a flu vaccine that exists, and we've seen very little data comparing the proposed vaccine to a currently

existing product.

And that gets to issues both of safety, where we really haven't seen head-to-head comparisons of safety, head-to-head comparisons of recurrent use of the vaccine, annual revaccination, and really very little on comparative efficacy.

And I guess it just really raises a question for the FDA about how we consider a new vaccine in the setting when there is one that is already approved and also even a more broader question about how if it is approved, a clinician would then go about making a decision about the use of these two competing products.

And so I guess, I think partly because of my previous experience on another committee, I'm just a little bit unsure about how we put a new product in comparison with one that already exists.

CHAIRMAN DAUM: Does FDA or sponsor want to comment on Dr. Parsonnet's issue?

DR. MIDTHUNE: I mean, obviously it's always interesting to have comparative data, but the primary requirement is that you demonstrate safety and effectiveness, and in this case it has been done in comparison with the NAF control, and that certainly is acceptable to us.

You know, clearly, I think that some of the evolving recommendations moved ahead of the development of this vaccine, and for example, since the adult study was, you know, done, you know, the ACIP subsequently made recommendations to recommend influenza vaccine for individuals above 50 years of age.

I think had that recommendation been in place at the time, we clearly would have asked actually for a comparative study in that particular situation because, you know, clearly sort of a standard would have been to give the inactivated vaccine, but that's not where we were at that time.

And also at that time, for healthy children, there was no recommendation for administering influenza vaccine. So perhaps that puts a little bit of the history into a context.

CHAIRMAN DAUM: To this issue? Dixie and then Dr. Katz.

DR. SNIDER: Well, I'll speak, you know, with my ACIP hat on and say that I think Dr. Parsonnet's points are well taken, and they are issues that are going to be highly problematic, and I'm sure subject of vigorous discussion not only of the ACIP, but the AAP and the American College of

Physicians and other professional societies that are going to have to, you know, weigh in on how they feel about the use of this particular product vis-a-vis the other available product and hopefully give some guidance to clinicians as to how to deal with the situation.

But they are very important points.

CHAIRMAN DAUM: Dr. Katz, this issue?

DR. KATZ: One, Julie, I don't think we ever demanded any studies of pneumococcal polysaccharide vaccine versus pneumococcal conjugate vaccine. The licensure of pneumococcal conjugate vaccine was on its own virtues and assets and not on comparison. That's a specific example.

A generic one is I think those of us who call ourselves vaccinologists are very interested in there being more attitude and aggression towards mucosal immunity, and I think the idea that mucosal immunization could in some ways supplant injectable vaccines is very appealing.

I have a slide that I wish I had brought with me which shows a 15 month old child being told that, well, there'll be one more injectable vaccine each year, and if you will forgive a nasty comment, this one year old is pictured going, "Not on your

life."

(Laughter.)

DR. KATZ: So that I think the people who complain that we're giving kids 20 and 22 injections in the first two years of life or the first five years of life have a lot of interest in mucosal vaccines, and especially as we talk about a vaccine that, if you believe in it and you use it, is going to be administered annually. The pragmatics of it become a major issue which the pediatricians have been discussing because somebody said this morning "recommended." It isn't yet recommended. It's encouraged for children six to 24 months of age.

But if that is followed, as many people anticipate by recommendation and not just encouragement, aside from the idea of another injection, the logistics for physicians who take care of children are rather formidable if you have the window from September to November to give a vaccine.

And the question arises: does it have to be given in physicians' offices? Can it be given in day care centers?

There are a lot of other things that

make us a lot more enthusiastic about the whole field of mucosal immunization rather than more injections.

CHAIRMAN DAUM: Thank you very much.

There's one more preliminary piece of business to address, and that is Dr. Mendelman asked me if he could show two slides to address the issue of Dr. Faggett, and that is minorities and others who might have been immunized with FluMist present or absent from the BLA database.

DR. MENDELMAN: Present. These are the demographic characteristics in the healthy working adult study. So most of the individuals were Caucasian, ten to 11 percent were black, and the median age was 38 across both groups.

In the 19 study, the Northern California Kaiser study, I don't know if we can move that up, but I guess you can see it. Ten, 11 percent Asian Pacific Islander, 20 percent versus 19 percent Hispanic, 55 percent Caucasian, and six percent African American, et cetera. This was Northern California. So it was primarily Oakland and the surrounding areas.

And the last one, and you have this in the briefing document from the FDA, I think the

request was also to look at efficacy by race, and the efficacy, Caucasian or non-Caucasian, 94.9 percent for any influenza and 92 percent for Caucasians in the pivotal efficacy trial in children.

DR. FAGGETT: One follow-up question, if I may. Do you have any experience in terms of emergency room visits of the various populations as well? Probably not. Is that available?

DR. MENDELMAN: We have the emergency room visits from the Study 19, the Northern California Kaiser, because one of the three settings that was analyzed for medically attended events were all emergency department visits within the 42 days after vaccination, and hospitalizations and any clinic visit.

DR. FAGGETT: Thank you.

CHAIRMAN DAUM: Okay. That completes our sort of preliminary break generated housekeeping issues. What I'd like to do is just literally read the first question now and then ask the committee for discussion of things that we haven't addressed that they would like to address before we actually begin our voting process.

So the first question, as I understand

it -- Dr. Mink, please correct me if I say anything wrong here -- has two parts, A and B. Part A is: are the data adequate -- it's a safety question, right? -- are the data adequate to support safety of FluMist for individuals in the three age groups that you see up there, five to 17 years, 18 to 49 years, and 50 to 64 years?

And to please consider the data relative to respiratory events, asthma, and URI, shedding and transmission of vaccine strains following receipt of FluMist, and annual revaccination.

And then Part B becomes relevant if you believe the data are not adequate for Part A, and that is: if the data are not adequate for specific age groups or if there are other safety concerns, please discuss what additional data should be requested.

DR. MINK: With the addition that it should say "healthy individuals."

CHAIRMAN DAUM: Yes. I even wrote that and I still forgot to say it. So it's normal people we're talking about in this question. So thank you.

Okay. So are there any other issues that we need to talk about to have an airing of the issues in this question? Dr. Stephens.

DR. STEPHENS: I'd like to have comments about the revaccination issue because this is going to be something presumably given every year, and yet at least from my understanding, the data for older children and adults really doesn't exist for efficacy, for example or in most instances safety for revaccination, and I'd just like to get a comment on the revaccination question because that's what we're going to be doing presumably with this vaccine.

CHAIRMAN DAUM: Let's get you a couple of comments. Let's hear from the sponsor, and let's hear from the agency as well.

DR. CONNOR: I think the primary revaccination data, as you point out, comes from pediatric trials. The data that we've provided for you shows both on the efficacy side, the second year efficacy of data, as well as on the safety side the data both from the AV006 trial and multiple revaccination years, and we also have data that looks at SAEs across those years and demonstrates that there isn't any difference and that generally things are lower in the reactogenicity cycle following multiple years.

It is a setting in pediatrics where

there is more reactogenicity generally than in the older population. So we believe that that represents the opportunity to best look at the issues of revaccination, but there's not specific revaccination data in the older populations. I guess those are just the SAE data.

CHAIRMAN DAUM: Dr. Mink, do you or someone else in the agency want to comment on that issue from your perspective?

DR. MINK: On the slides that I showed, slide number 18 shows the total database. It shows that across all age groups there was 7,354 second dose experienced with FluMist. I believe it's page 5 on your handout, slide 18. Those are the revaccination data for second dose.

You can see that about 3,000 of those are in one to four years of age; 2,600 are from five to eight years of age; and just over 1,000 are in children from nine to 17 years of age. So those are the total number of subjects in the database with repeat vaccinations.

However, in the second dose for some of the kids, those will be the same dose in the same year. They're not all a second year or a second season.

For subjects in the AV006 trial, we do have the repeat vaccination data for safety and efficacy in year two and safety data from year three, which I presented, and then also for individuals over ten years of age there are some vaccinees in study AV012. I believe there was a total of 2,100 subjects in AV012 who received doses in two years. We have SAEs mostly from those individuals, and there was no increase in the repeat vaccinees.

CHAIRMAN DAUM: I trust that reviews the available data and addresses Dr. Stephens' question.

Other questions specifically focused on question one?

(No response.)

CHAIRMAN DAUM: Okay. So, Dr. Stephens, you are in the hot seat for the last time probably and perhaps you could initiate our discussion of question one.

Now, I should say as a procedural item that I have a voting sheet somewhere, right in front of me, and that we will record your vote separately for each of these age groups so that when you're finished speaking I'll know how you felt about five to 17 years, 18 to 49, et cetera, and then your

comments regarding question B will be recorded as well.

Then once we complete this, we'll then put up question two and again look at discussion issues and we'll repeat the process till we're done.

Dr. Stephens.

DR. STEPHENS: A couple of kind of opening comments. One, I think there's been a lot of progress made since we first heard about this vaccine a year and a half or two years ago. I think there's pretty convincing data in terms of the new analyses that the vaccine does have a problem in kids under five in terms of potentially probably at a small rate increasing the incidence of asthma and croup. I think that's certainly borne out by the new analysis of the data.

In older individuals, I think that's probably not the case. There is evidence of viral shedding. There is evidence of transmission, but I am somewhat relieved by the data that's presented today in terms of certainly the transmission issue.

The issue of reassortment, I think, is still on the table, and I preface all of that by commenting on the safety categories.

I think the one kind of issue that we're

facing is that this was a vaccine largely designed initially for children, young children, and now it's kind of being reassessed, if you will, and relooked at for older groups, and I think that the problem that we run into in some of these age categories is lack of specific data about the specific vaccine.

So from my perspective, and I'll start with what I think are the easy categories first, the 18 to 49 year old, I think there is data that is adequate to support the safety of FluMist in healthy individuals in that particular age group.

I think also that there is reasonable data in the five to 17 year old age group. My concern is actually that five to nine group where the issue of asthma may not be completely solved at least in my view, but the data would suggest that in all likelihood, and I would probably vote yes, that in five to 17 year old individuals that there is adequate data for safety in the individual, in the healthy individual.

I don't think thought that with an n of 500 or so, 511 I think it is, that there is good data in the 50 to 64 year old age group for safety, and I think that's largely an issue of numbers.

For individuals undergoing

revaccination, we just heard that data represented. I think it's more of an issue of efficacy than it is safety. So I would probably vote yes in terms of safety for this category.

I think there continues to be though concerns about this attenuated virus in terms of reassortment issues, in terms of introducing this into a very large population, a very large amount of this vaccine being administered to the population, and we'll come to -- so that remains an issue in my mind.

And I think I'll stop there and turn it over to Dr. Katz.

CHAIRMAN DAUM: Before we leave you, I heard three yes votes for the different categories.

DR. STEPHENS: You heard yes, yes, no, and yes.

CHAIRMAN DAUM: I end up confused. I apologize. No, it's good we get this straight in the beginning and then it will go well.

DR. STEPHENS: For the age group -- there are four questions here as I read it -- five to 17 year olds.

CHAIRMAN DAUM: Correct. Eighteen to --

DR. STEPHENS: And I would vote yes.

Eighteen to 49, yes; 50 to 64, no; individuals undergoing annual revaccination, yes.

CHAIRMAN DAUM: No.

(Laughter.)

CHAIRMAN DAUM: What I think we've been asked to do is --

DR. STEPHENS: It looks like I'm working from an older version of this particular question.

CHAIRMAN DAUM: Yes, the newer version is what we were showing this morning.

DR. STEPHENS: Okay. Three age groups: yes, yes, no.

CHAIRMAN DAUM: Okay.

DR. SACHS: Everybody has a newer version in your packet, your folder, your blue folder. So it should be more than one page, and we'll all work from the same version.

CHAIRMAN DAUM: I think we're there now. Now I understand what happened. Okay. So it's good to straighten these things out early because then we streamline the process and it gets much easier.

So Dr. Katz.

DR. KATZ: Dr. Katz has an initial question, which is: who came up with these age divisions and on what basis?

I don't understand how we divided the life span from five to 64 into these three groups. I don't know of any other vaccine where we've ever studied in that particular way.

I tried to think. This is a live attenuated vaccine, and I tried to think of the other live attenuated vaccines we use: measles, mumps, rubella. No one has ever shown any difference in age groups with measles or mumps. With rubella, yes. Post menarcheal females are more apt to have arthralgia. That's the only thing I can think of.

OPV, when we used oral polio vaccine, which as my colleague has pointed out we don't use anymore fortunately, there was a suggestion in very early years that perhaps people over 18 were more likely to develop vaccine associated paralysis, though that was never borne out.

Yellow fever vaccine? Dr. Snider has brought us information at the last meetings on adverse events in adults, but I don't think many children get the vaccine. So the denominator doesn't give us any data on which to base. So I'm left with a basic question: why should I have to worry?

Vaccinia, which we're thinking very seriously of using again. The very young child in the first two years of life perhaps has a higher rate of adverse events, but you get above that and there's no difference among different age groups.

So I find it very difficult to get excited about differentiating. So I'd vote yes for all three.

DR. MINK: Dr. Daum, may I answer?

CHAIRMAN DAUM: But of course.

DR. MINK: The reason the 50 to 64 year age group has been divided out is because of the CDC acknowledgement of them being high priority because of the significant percentage of those --

DR. KATZ: Yeah, but there's nothing to suggest that they're at higher risk of adverse events.

DR. MINK: I'm just explaining to you why the questions are presented to you by these age groups.

DR. KATZ: Okay. I don't accept that as justification.

(Laughter.)

CHAIRMAN DAUM: I have a suspicion that we are not going to resolve this issue.

(Laughter.)

CHAIRMAN DAUM: Right here and right now, and so we're going to move on and hear from Dr. Edwards.

DR. EDWARDS: I think for many of the same reasons that David articulated, I think that the five to 17 years' safety data is quite extensive, as is 18 to 49, given the data of the effectiveness trial.

I'm less comfortable, however, with the data from 50 to 64 in terms of safety primarily because of the numbers and because that this has been a group that has been looked at and targeted as many of their members in higher risk groups.

So I would like to vote yes, yes, and no.

CHAIRMAN DAUM: And can you address Part B also? I think I mischarged the committee a little bit because you can answer Part B if there are other safety concerns, even if you felt the data were adequate.

So do you have any Part B issues?

And, Dr. Katz, if you did, you could pipe up as well.

DR. KATZ I think with Part B I would

only add that there should be continuing studies of transmission.

CHAIRMAN DAUM: Thank you.

Dr. Edwards?

DR. EDWARDS: I think the transmission issues obviously need to be looked at, and I think as we're going to come back to in post marketing, there has to be attention to reactive airway disease and asthma in post marketing.

But I think that other than that currently we're safe.

CHAIRMAN DAUM: Thank you very much.

Dr. Snider.

DR. SNIDER: I think I'd generally agree with my colleagues who have spoken thus far. I think the problem of asthma, reactive airways disease is potentially a problem for those less than five, and it may be a problem of lower frequency in older age groups.

At the same time, as I mentioned earlier, unfortunately we don't have the data to know whether what might be precipitated by FluMist is less than what would occur with natural infection. We don't know if TIV, as far as I know, really protects against asthma reactive airways

disease as well as FluMist might do it because we don't have a head-to-head comparison on that.

So I think the point is it's an open issue and one that needs to be studied in more detail.

As far as the specific questions about the age groups, I'm comfortable with the safety data for the five to 17 year age group and the 18 to 49 year age group. The 50 to 64 year age group, I think it's 511, and I would prefer to see a larger population.

I think with regard to additional concerns I don't have huge concerns about transmission. I don't have huge concerns about reassortment. There are these things we've talked about in terms of inadvertent administration to people in whom it would be contraindicated according to the current application and high risk people who might receive it because of transmission.

So I think additional studies there are indicated, but I don't have a high level of concern about it.

The revaccination issue has already been clearly outlined. I think the data there indicate a high level of safety in the younger age groups. I

can't think of biologically plausible reasons why that would be a major problem in the older populations, but the fact is if we look at the data submitted under the BLA, we don't have data, extensive data, on revaccination. So that's additional data that would be nice to have somewhere along the way.

And that's all I have to say about question one.

CHAIRMAN DAUM: Dr. Snider, so I understand you, in the 50 to 64 you voted no?

DR. SNIDER: Yes, yes, no.

CHAIRMAN DAUM: Thank you very much.

Dr. Hamilton.

DR. HAMILTON: Yes, yes, no.

With respect to considering the additional data, I think that one merely has to look at the numbers in the study design and the confidence is related to that, but more of the studies were designed to look at respiratory events, and by necessity perhaps shedding and transmission received a lot less attention, as did annual revaccination. And perhaps additional data should be generated to reflect that.

CHAIRMAN DAUM: Thank you very kindly.

Dr. Eickhoff, the time has come.

DR. EICKHOFF: A year and a half ago I think I voted no on the safety issues, and I'm going to change my vote this year.

For the shedding and transmission data, sure, I think that should be studied. We need further studies of that. I'm less concerned about transmissions to the high risk host simply because wild type influenza by and large is not seen as a problem in immunocompromised hosts, including those who are organ transplant recipients and including those who have AIDS, for example.

We don't see serious disseminated disease in the same way we see serious disease if they are exposed to other live attenuated viruses like MMR or varicella or perhaps all too soon vaccinia. So I am less concerned about transmission to a high risk host. It's going to be less of a problem than it is with wild type influenza.

Annual revaccination? Yes, again, I would like to see more data about that as the years go by. There is some data with regard to annual revaccination of TIV, but again, not that much. So as cold adapted influenza virus comes along, I think that's a subject for further study.

Asthma has been identified as a problem in the one to five year olds. There may be a problem. I'm not convinced it is a problem, but the answer will come from comparable studies of wild type influenza studied in the same way as these individuals who have received CAI vaccine were studied.

It may not be intrinsic to this vaccine. It may be intrinsic to influenza viruses in general.

Given all of that, for safety in the first two age groups, I will say yes to both of them. The 50 to 64 year old age group, if I could think of any biologically plausible reason why they might behave different immunologically from those ten years younger, I might hesitate, but I can't think of such a reason. So I will vote yes.

CHAIRMAN DAUM: Thank you very much.

And we'll go on to Dr. Cox.

DR. COX: Yes, I would like to, first of all, say that both the sponsor and the FDA have made our lives so much easier. Although we're awash in data, we have been pointed in the direction, and it's just much easier than dealing with the information that we had last time.

So for the first three questions, I

would say yes, yes, and yes.

With respect to the 50 to 64 year old age group, I agree with Ted and with Sam. I cannot think of a biologically plausible reason why the safety would differ in this age group.

I think that the additional studies that I would like to see done have to do, first of all, with developing tools that could be used by practitioners to screen out those with high risk conditions so that we can be sure that those with high risk conditions are receiving trivalent inactivated vaccine.

I think we do need continuing studies on transmission, reassortment, and genetic stability, and I would also like to see additional information generated on annual revaccination both in terms of safety and efficacy.

CHAIRMAN DAUM: Thank you so much.

Before we go on, I'd just like to remind everybody that there is some confusion, and the preliminary questions are not what we're using today. We're using the questions that are here. So there are really only three age groups to address.

And I presume from the global tone of your comments that you voted yes on all three, but

please correct me if I'm wrong.

DR. COX: Yes, I voted yes on all three.

CHAIRMAN DAUM: Yes, but I think David Stephens got a little confused by that as well, but were using this version of the questions today. So committee members could try and remember that.

Dr. Gellin.

DR. GELLIN: I'll assume that was so I didn't screw this up as well.

Since the question is are the data adequate, I'll stick to that question, and for that reason will vote no on the older category, 50 to 64, but yes on the two younger categories.

I think, I mean, somewhat along the lines of Sam about the age stratifications. I actually would like to see subsequent data better represented in children nine and above and less than nine, particularly since the recommendation for those less than nine will be two doses. So I think that has some relevance to the annual revaccination issue.

CHAIRMAN DAUM: Thank you very much, Bruce.

We'll move on to Dr. Steinhoff, please.

DR. STEINHOFF: I'm going to vote yes on

all three groups, but I want to raise an issue that's been raised before in a slightly different way, and I'm concerned about the issue of transmission to household members who might be at high risk, and I don't know quite how this should be dealt with, but one approach might be the obverse of the recommendations for the inactivated vaccine is that it should be given to healthy persons who are in a household with persons at high risk who would also get the vaccine.

You might want the observe of that, that this vaccine maybe should not be given to persons who have household exposure to subjects at high risk.

That's not too confusing, right? Who are also unvaccinated. What I'm trying to say is we need some more data on the actual transmission and risk in the likely common household exposures to people who get this vaccine.

CHAIRMAN DAUM: Mark, thank you.

We'll move on to Dr. Myers.

DR. MYERS: Well, I'll start off by saying I don't like the questions because I agree. I think the age stratification is not the way it should be. It should be eight and below and eight

to 17 and 18 and above.

With that said, like Mark I have concern about the transmission within households when we have remarkably little data on people with underlying diseases, and so let me take 1(b) first.

I think there needs to be more safety data collected on the 50 to 64 year age group. I think there ought to be specifically data collected on safety in individuals with chronic diseases, particularly chronic lung disease.

I think there should be a comparative trial to trivalent inactivated vaccine, and the question I would like to have been asked but we weren't asked was do I think there's sufficient data on annual revaccination. My answer would have been no, that I don't think there is.

We're talking about this vaccine used year in and year out, and we just have no data except for two or three doses to children. So I wasn't asked that question, but I'll give you the answer anyway.

CHAIRMAN DAUM: Thank you very much.

DR. MYERS: So my voting would be I believe the data does support the safety of FluMist in healthy individuals five to 17, 18 to 49, and 50

to 64, and for the same reasons that Sam does, I can't think of any reason why 62 year olds are different than 49 year olds.

CHAIRMAN DAUM: Thank you very much, Dr. Myers.

Did you want to say something?

DR. MYERS: No.

CHAIRMAN DAUM: Okay. Moving right along, Dr. Overturf.

DR. OVERTURF: I would vote yes, yes, and yes, based upon the fact, again, I do not feel there's any biologically plausible reason to expect differences in the 50 to 64 year old age group.

I also think that for all the questions below regarding data for respiratory events and shedding and transmission of the vaccines and annual revaccination there's a critical need for a lot more data and will have to be a critical part of the post licensure evaluation of this vaccine.

I'm also a little bit concerned about what the demand for this vaccine might or might not be, and that it would be interesting to see in the future how the production of the vaccine which has to be done on an annual basis -- it seems rather complicated to me -- will be able to keep up with

that demand.

Obviously part of that will be dependent a little bit upon how the ACIP and other professional groups decide how to recommend this vaccine or whether they choose to recommend it or let people decide for themselves whether they want to take this vaccine.

I think there will be, because of a lack of education, a lack of data, a critical need for serious education of individuals who choose to take this vaccine over another vaccine which already has a safety and efficacy profile defined for it. So I think that's going to be a critical role for professional bodies in the future to try to define this for potential vaccinees.

CHAIRMAN DAUM: Dr. Diaz

DR. DIAZ: I would vote yes, yes and no, and purely from taking the purist standpoint in answering the question is the data adequate to support safety. I think we're splitting hairs in a sense because it really comes down on that last question to whether one is willing to extrapolate from the data that's presented.

I think the sponsor did a good job of looking carefully at the data in the 50 to 64 year

old age group that they had, and in my mind I don't think that there's any reason to suspect likewise that there would be any ill effects safety-wise in that age group.

But based upon the question and the small n, my vote would be yes, yes and no.

I do think there's more need for information on transmission and reassortment. In particular, I would very much like to see a movement toward capturing information on annual revaccination not only with this vaccine, but also with the inactivated flu vaccine because there isn't much data, and we're using it in younger and younger populations where the accrual rate over time in terms of revaccination events is going to be much higher than it was in the past.

So I think there is a need to get information on revaccination on an annual basis.

CHAIRMAN DAUM: Thank you very much.

Dr. Faggett, please.

DR. FAGGETT: Yes. Starting with B first, I really would like to see some other data relative to populations in other geographic locations, such as the TennCare population that Dr. Edwards mentioned earlier. I think that there are a

lot of differences not just with ethnicity, but socioeconomic status that you probably won't capture in a closed system, health care provider population.

Saying all of that, I do vote yes, that the data is barely adequate for five to 17, 18 to 49 and 50 to 64. So yes in all three.

We do need more studies in terms of shedding and transmission of the vaccine strains. I think the jury is still out in terms of annual revaccination.

CHAIRMAN DAUM: Dr. Faggett, thank you very much.

We'll go on with Dr. Markovitz, please.

DR. MARKOVITZ: Yes. For the reasons outlined already by Drs. Katz, Eickhoff and Cox, I'd vote yes, yes, and yes. In 1(b) for data that we need, clearly besides whatever else we need for these age groups, and I do believe it's very important to vaccinate healthy people in these age groups, we need a lot more data on older people and people with underlying problems who, of course, are the absolute top priority for flu from a public health point of view. So that's what I'd like to see more of.

CHAIRMAN DAUM: Thank you so much.

Dr. Parsonnet.

DR. PARSONNET: I'm also going to vote yes, yes, and yes. I think they looked at the study to look at 18 to 64 and showed that it was safe from 18 to 64 and doing a post hoc subgroup analysis of 50 to 64, they just need to really show that it's comparable in those age groups, and otherwise they could take out each individual year. Fifty-one, is that safe? Fifty-two, is that safe?

I mean, you can't even looking afterwards for these post hoc analysis, I think it should be -- unless we have some reason to think otherwise, it should be considered safe in those groups.

I'd like to see more comparative data with the currently available vaccine in terms of safety because I think it will help in making decisions for various groups in using these vaccines in the future. I'd like to see more data on smokers and safety in smokers.

And I don't think biologically it's likely that there are really going to be safety issues with revaccination, but it would be nice to see more revaccination data and more data in the elderly population.

CHAIRMAN DAUM: Thank you very kindly.

Ms. Fisher.

MS. FISHER: No, no, and no.

The data are inadequate to support the safety of FluMist for individuals five to 64 years of age. The increased risk of asthma in young children and the increased risk for some children in these studies for upper respiratory infections, musculoskeletal pain, otitis media and croup, as well as upper respiratory symptoms in adults suggest that an unknown number of health, but perhaps genetically vulnerable individuals across all age groups will not be able to handle this vaccine well, and this will over the long term also lead to the public perception that when you get the flu vaccine you get the flu.

And this is an important consideration long term because when you make healthy people sick after they get a vaccination, whether it's with live virus polio vaccine or live virus flu vaccine, when you have inactivated vaccines that do not cause disease symptoms, you're going to pay a price in terms of the public perception of the risks associated with vaccination.

You were able to successfully make the

argument to prevent polio, but as I said, flu is not polio, and because most healthy children and adults are not permanently injured or die from the flu, I think careful thought needs to be given to this issue.

The fact that live vaccine flu virus is shed in 80 percent of recipients poses an additional risk for our population at large, particularly for immune compromised individuals across all age groups.

The outstanding questions about the true rate of transmission of vaccine strain viruses among children needs to be clarified, as does the retention of the attenuation of the shed viruses and the high frequency of nucleotide changes. Because this live virus nasal vaccine is not indicated for high risk health groups, which have historically been the targeted population to receive the flu vaccine, it's a very serious step to move to use of a live virus vaccine for the majority of healthy individuals, and a standard for proof of safety must be very high.

I don't think that standard has yet been met by the data which have been presented so far. I'd like to see a trial of a genetically diverse

group of American children and adults which addresses safety and efficacy of simultaneous vaccination with FluMist and other vaccines, revaccination, vaccine shedding, and the rate of household transmission to the unvaccinated individuals, as well as genetic stability.

CHAIRMAN DAUM: Thank you, Ms. Fisher.

We'll move on to Dr. Goldberg.

DR. GOLDBERG: Okay. I guess yes for five to 17 years, recognizing that I think that in the younger age groups here it's not clear to me that there may not still be some effects that are continuing on from what we saw in the younger children. I do believe we made the right recommendations the last time, that there were problems with the younger children that have been borne out.

Eighteen to 49, yes.

Now, I don't believe in post hoc subgroup analysis, but that said, I do think that there really are inadequate data for 50 to 64 if we're going to split the hair and label it in that way. So my answer would be no.

I think we need more information, more trials on shedding and transmission and

reassortment, as well as annual revaccination studies.

CHAIRMAN DAUM: Dr. Goldberg, thank you.

I guess it's my turn. I'd like to compliment the company and the agency team working together on the progress that's been made sine the last time we've heard about this vaccine. Many of the anxieties and concerns, not all, have been addressed adequately, in my opinion.

I think that the decision to move the requested indication to age five, an age when we currently don't actually immunize healthy children against influenza, was a bit of a master stroke in terms of corporate strategy because a lot of the issues in children under five were swept off the table.

I believe that the answer should be yes on the safety data across the board. Having said that, I would like to see more data generated by the company's sponsorship working together with the agency's guidance.

The shedding issue is an important one to me, and I think we don't know enough about it, and we don't know enough about the impact on the people on whom the virus is shed.

Having said that, I'm persuaded that this is a relatively low frequency event, a relatively low inoculum event, and is, after all, an attenuated virus.

The concurrent vaccine issue, of course went by the boards by and large with the moving the lower age to five, but there are adults who will get simultaneous vaccines, particular vaccines against pneumococcal disease, and so there are some issues there that I would like to see explored, but I don't think that's an issue for holding this up at this point.

The annual revaccination issue that several have addressed is obviously a very important one and needs additional information. I'm always persuaded by Dr. Faggett's argument that there aren't enough minorities. We saw especially in populations where people were likely to come back and likely to comply, and I think that the real world contains large segments of people who aren't, period.

And we need to make sure that the vaccine performs in those settings as well, and I'd like to at least have some safety data generated in the future about those.

I'm also intrigued by and persuaded by Dr. Cox's suggestion that we know more about the molecular documentation of the transmission and genetic stability of this virus, but I think we saw enough data that I feel confident that this won't be a deal breaker, so to speak.

So I'm willing to vote yes on all three of these issues, and with those 1(b) issues that I raised.

And that brings question one to a close.

Say it again, please.

DR. FREAS: Industry's position on record.

CHAIRMAN DAUM: Industry's position for the record, but of course.

Dr. Decker, would you give us industry's position, please?

(Laughter.)

CHAIRMAN DAUM: As best you can.

DR. DECKER: No, I can't do that, and let me take this opportunity to clarify. I'm the industry representative, but of course, I'm Michael Decker. I'm not some distillation --

CHAIRMAN DAUM: We know that.

DR. DECKER: -- of industry. All right.

So let's be clear on that.

Also, because it did come up, let me comment that you can't have an industry rep. who represents the industry who is not involved in industry. So it is inevitable that as long as there's an industry rep. there will be discussion here of products that that representative has something to do with.

In this case, I think everybody knows that I work for Aventis Pasteur, which is the world's largest manufacturer of inactivated influenza vaccine.

This arises all the time at these meetings. So I also hope everybody knows that when I make comments, at least I think they're solidly grounded in the scientific issue, and they're not simply trying to stroke either Vanderbilt, one hat I wear, or Aventis Pasteur, the other hat I wear.

So with that preface out of the way, my comments have all been articulately spoken by the members of the committee. I really truly have nothing to add to what's been said here.

CHAIRMAN DAUM: Most unusual in my experience.

(Laughter.)

DR. DECKER: It's a going away present for you, Bob.

CHAIRMAN DAUM: Michael, we are mindful of the difficulties that you find yourself in, speaking for, quote, all of industry and at the same time obviously a member of one specific company, and we appreciate your candor with respect to that.

I know Dixie wants to make a comment, but before I call on him, I'd like to announce the results of the vote on question one. The question concerns the adequacy of safety data for individuals in three age categories.

For the first category, age five to 17, the committee voted 17 to one that the data are adequate.

For the second category, 18 to 49 years, the committee voted 17 to one that the data are adequate.

For the third category, 50 to 64 years of age, the committee voted ten to eight that the data are adequate.

That is the vote on question one, and before we move on, Dixie, let's hear your comment, please.

DR. SNIDER: Well, my comment had to do

with the 50 to 64 year age group, and what I wanted to make clear is that from my perspective if we're talking about this question in a purist sense, in a sort of abstract way, in other words, healthy people 50 to 64 years of age, I would have no problem voting yes.

The difficulty I see, being a pragmatic person, is that when people were talking about biologic plausibility, people 50 to 64 years of age begin to get in significant proportion a number of chronic health problems, and the question becomes: can you effectively screen those people out?

And I would submit that you don't always successfully do that. And so from a pragmatic standpoint, I'm comfortable with those numbers, realizing the pragmatic difficulty of trying to actually identify a true healthy population.

CHAIRMAN DAUM: Thank you very much, Dixie.

I'd like to ask that question two -- oh, look at that. Okay -- be put on the screen and begin by asking committee members if there are issues that they feel like haven't been discussed today that they need clarity on before we start the voting process. Question two, are the data adequate

to support efficacy of FluMist in individuals in the same age groups as we saw before, Dr. Katz demurring perhaps and others?

And then if the data are not adequate, what additional data should be requested? So are there discussion issues unaddressed?

Dr. Edwards.

DR. EDWARDS: I guess that goes to say to support efficacy/effectiveness, right?

CHAIRMAN DAUM: FDA, comment, please.

DR. MIDTHUNE: Yes.

DR. EDWARDS: Yes.

CHAIRMAN DAUM: Dr. Midthune says yes.

And also we add the word "normal" or "healthy" to the question again, correct? Again, yes.

Okay. So there's two clarifications there. All right. David, let's go.

DR. STEPHENS: Thank you, Bob. I appreciate it.

CHAIRMAN DAUM: If I ever come back as a guest, you know where I do not want to sit.

DR. STEPHENS: You know where you're going to sit though.

(Laughter.)

DR. STEPHENS: My votes are yes, yes, and no on these three age groups. I certainly think based on the effectiveness data that the 18 to 49 year old group, there is evidence of effectiveness, and I interpret that to be efficacy.

I'm bothered by that to some degree, but I'm willing to accept it for that age group.

I'm a little more concerned about the younger age group. We really don't have a lot of data on the, say, ten to 17 group. In fact, there's very little data, but I'm prepared to, looking at the efficacy data across the board in the older studies to accept the fact that for this age group that there is reasonable data to suggest or indicate that there would be efficacy of FluMist in healthy individuals.

I am concerned about this issue which has been raised about whether we would use FluMist or whether we would use an inactivated vaccine in this particular cohort of individuals, and we have no head-to-head comparison, and I think that, again, the data on 511 individuals regarding efficacy -- and I appreciate the arbitrariness of breaking out this age group, but that's what we've been asked to do, and that's what the ACIP has now done in terms

of the recommendations for inactivated influenza in this particular group.

So I appreciate that, as he's saying, without any doubt. But I'm --

(Laughter.)

DR. STEPHENS: I remain concerned that this is a group that we do not have adequate efficacy data, and rather than give FluMist versus the inactivated, I think we need a study to address that particular issue.

CHAIRMAN DAUM: Thank you very much.

Dr. Katz, please.

DR. KATZ: I may surprise Dr. Stephens by somewhat agreeing with him because now I turn the question not to safety, but to efficacy, and there certainly is suggestion that with advancing age there is loss of immunologic responsiveness to various antigens.

I'm very comfortable in the younger groups beginning at age five. A lot of data on five to six years of age is all we know about the immune system. It's mature at five years of age, and I think we can, to my way of thinking, extrapolate from that on through healthy adult life.

When you get up into -- and again, it

has been an arbitrary decision which I had no vote on -- but when you get up into the 60s, you begin to get people who don't respond to vaccines. Again, we're talking about a live vaccine, not an inactivated.

Who doesn't respond to Hepatitis B vaccine? Inactivated admittedly, not live, but it's the older age group. As you get older, as you smoke, as you're fat, you're less likely to respond to inactivated antigens.

I don't know about this. So that I guess I would vote yes, yes, no, requesting more data on immunogenicity. I'd settle -- you should forgive me -- for antibody data.

(Laughter.)

DR. STEPHENS: Which may be easier to collect than efficacy data.

CHAIRMAN DAUM: Thank you very kindly.

Dr. Edwards.

DR. EDWARDS: I have similar conclusions. I think that the revaccination issue is more important for efficacy effectiveness because I think we do know that the more antibody that you have either locally or humorally, the less you're going to respond to the cold adapted vaccine. So I

think that really does need to be looked at, the revaccination question in terms of efficacy and effectiveness.

So I would vote yes, yes, and no in terms of the efficacy/effectiveness.

CHAIRMAN DAUM: Moving right along, Dr. Snider.

DR. SNIDER: I would agree and vote yes, yes, and no, and point out that if you're going to do that study, you can also get some additional safety data in 50 to 64 year olds.

CHAIRMAN DAUM: Could you clarify what study you mean, for the record, Dixie, please? The question contains a hook at the end of it. What additional data are requested? And you said if you're going to do that study. So what --

DR. SNIDER: If you're going to study efficacy of the vaccine against placebo and/or with the inactivated vaccine, it gives you an opportunity to look at additional safety data in that large group.

CHAIRMAN DAUM: Thank you.

Dr. Hamilton.

DR. HAMILTON: Yes, yes, no, and I agree to study older people.

CHAIRMAN DAUM: Dr. Eickhoff?

DR. EICKHOFF: Yes, yes, and yes. Yes on the third age category simply because I think the distinction between those two adult categories is artificial and not biological.

Just one other comment. I appreciate Dr. Nichol's justification for the effectiveness study. By and large in pre-licensure studies, however, I vastly prefer efficacy studies.

CHAIRMAN DAUM: Thank you. Before I call on Dr. Cox I'm going to call on Dr. Overturf because we're beginning to run into airplane schedule problems and ask him to weigh in next.

DR. OVERTURF: I would vote yes, yes, and no, based upon I think there are some biological differences in the older adult, and I think there's precedent in other studies. So I think there needs to be more data.

I think the data could be more easily obtained by efficacy rather than effectiveness data and could be done in a smaller group probably. So although I think either study would be useful in that group, certainly I think true efficacy would be a better study and easier to obtain perhaps.

CHAIRMAN DAUM: Thank you, Dr. Overturf.

We're going to return now to Dr. Cox. Sorry and thank you.

DR. COX: Sure. I would vote yes, yes, and yes. I think that while there are immunologic differences in older age groups, I think that they apply both to an activated vaccine and to the live attenuated vaccine.

And I would suggest that annual revaccination studies are particularly important with respect to efficacy.

CHAIRMAN DAUM: Excellent. Thank you.

Dr. Gellin.

DR. GELLIN: I seem to be hung up on the E words here of efficacy, effectiveness, and extrapolation, and while I was tempted, you know, the changing of the question to make it, slash, effectiveness, I think it's actually a pretty significant inclusion in the question, particularly for a new product, and it strikes me that this is a precedent setting inclusion in that question.

Nevertheless, my vote would be yes, yes, and no because I know the effectiveness data is interesting. I'd like to see a formal efficacy study of all the population.

CHAIRMAN DAUM: Thank you, Bruce.

Dr. Steinhoff, please.

DR. STEINHOFF: I would mark this yes, yes, and no.

CHAIRMAN DAUM: And therefore, we ask for Part B comments.

DR. STEINHOFF: Right. Additional data on the efficacy in the older group.

CHAIRMAN DAUM: As opposed to effectiveness. Thank you.

Dr. Myers.

DR. MYERS: I'm going to vote no, yes, and no. I think the efficacy data is for five and six year olds. There is no data for seven or eight to 17 year olds. I don't think you could extrapolate from a 49 year old effectiveness data into the eight year old population or to children who are getting two doses of vaccine, and so I don't believe that effectiveness or efficacy has been demonstrated for that age group.

Yes on the 18 to 49. I think Dr. Nichol made a good case for the effectiveness study.

No, I think there were several other people who have already made the point that I think that the 50 to 64 year age group could be less immunologically responsive.

So I think we need studies of the eight year old to the 17 year old for at least effectiveness or at least seroconversion, and I think there needs to be studies of trivalent vaccine versus FluMist versus placebo in the 50 to 64 year age group.

CHAIRMAN DAUM: Thank you very much, Marty.

Dr. Diaz, please.

DR. DIAZ: Yes, yes, and no, for the same reasons that Dr. Katz raised, especially in an older age group where the efficacy of the product, it would be nice to have some comparison data, a little bit more data in that age group in comparison to the efficacy in that age group for the inactivated vaccine.

CHAIRMAN DAUM: Dr. Faggett, please.

DR. FAGGETT: Yeah, this is becoming the cat's corner. I vote yes for the five to 17; yes for the 18 to 49; and no for the 50 to 64. I do agree we need more studies in the 50 to 64 age group and more comparative studies, as well.

CHAIRMAN DAUM: Dr. Markovitz.

DR. MARKOVITZ: Yeah. On the easy ones I'd like to vote yes for five to 17, yes for 18 to

49. For 50 to 64, while I believe more data would be helpful, and especially a direct comparison, again, in this age group and people who are yet older with the inactivated vaccine, I think if one had to extrapolate, there is, again, I don't think any biological reason why a 49 year old and a 55 year old are that different.

I also think that if anything, an older person is more likely to respond to the live vaccine than they would to an inactivated vaccine based on sort of general immunologic principles.

And then lastly, there's certainly old data that we haven't seen as a committee, but there are old papers showing the efficacy of previous iterations of this vaccine that's quite efficacious in yet considerably older people than 64.

So I believe that it's quite likely to be efficacious in the 50 to 64 age group, and while I'd like to see more studies, I vote yes in that age group also.

CHAIRMAN DAUM: Thank you, Dr. Markovitz.

Dr. Parsonnet, please.

DR. PARSONNET: I agree with Dr. Myers. No, yes, no. I think if you're thinking about

potentially giving this vaccine to millions of children, I'd like to see some data in that age group, and there's really no data in children between the ages of six and 17, and so I'd like to see some data about efficacy in that group.

In terms of the subgroup analysis from 50 to 64, again, I'm not a big fan of subgroup analysis, but when you have a subgroup analysis that actually kind of pushes you in the opposite direction of the main group analysis, you have to take it somewhat seriously, and so I say no to 50 to 64.

CHAIRMAN DAUM: Thank you very much.

Ms. Fisher.

MS. FISHER: I think the data support efficacy for children ages 60 to 72 months, but are inadequate to demonstrate efficacy for healthy children and adults older than 72 months. I think another trial including healthy subjects in all age groups should be held, and ideally it should compare the efficacy of the live virus vaccine to the inactivated vaccine, including what happens after revaccination.

CHAIRMAN DAUM: Thank you, but we will need your vote on the question. So I'm going to --

MS. FISHER: No, no, no.

CHAIRMAN DAUM: Thank you.

Okay. Dr. Goldberg.

DR. GOLDBERG: Okay. No for the five to 17 year olds based on the need for that extensive extrapolation beyond the 72 month data.

For the adult trial, I'd just like to make a comment. The primary endpoint that was specified was any febrile illness. In neither the entire cohort or the 18 to 49 or the 50 to 64 met that standard compared to placebo as being significantly better than placebo.

That said, all of the supported endpoints do hang together and do support effectiveness in the 18 to 49 year olds, but I don't believe they do in 50 to 64 year olds. So it's yes and no.

And I think we need a study comparing FluMist to the inactivated vaccine in the 50 to 64 year olds, and we need to think very carefully about what the endpoint does need to be. I certainly, based on these data, would not recommend that we do another study on any febrile event.

So that said, and then in the younger children you need to do an efficacy study.

CHAIRMAN DAUM: So to make sure I have it right, you're no, yes, and no.

DR. GOLDBERG: It's no, yes, no.

CHAIRMAN DAUM: Okay. So I guess I'm the last one here, and I'm concerned about a number of things. One is that there aren't any real world data with H1N1 viruses in any population.

Secondly, that we don't have good efficacy data in the six to 17 month old age group. I think we do have good efficacy data for the 18 to 49 year old group, and I can solidly vote yes on that part.

So I come to I think it's -- I don't remember whose issue it was -- but whether the -- Dr. Katz's issue -- whether the younger children, the five to 17 year old ones, can be extrapolated knowing that there's efficacy in even younger children and in older people.

And I think that the answer to that is yes, that they can be, and so I'm going to vote yes on that, although I would also prefer to have had more direct efficacy data in that age group, and perhaps one way to reaffirm that my vote is correct would be to get some antibody data in those children.

Then comes the 50 to 64 year old age group, and here I really am a little more nervous about assuming efficacy. On the other hand, we've been asked about effectiveness as well, and I think effectiveness was demonstrated.

So that I'm going to vote yes for that older group, but it's a back door yes, reasoning leaning on the effectiveness issue rather than efficacy.

So I'm going to end up with yes on all three, but I would really like to have more data, particularly in the elderly -- 50 to 64 is elderly. I hope I'm not offending anybody -- age group, and I think that antibody data would be very helpful, and perhaps it could be constructed to bridge to the inactivated influenza vaccine.

So that concludes, I think, the committee's vote, and let me just rub shoulders with Jody here for a second.

(Pause in proceedings.)

CHAIRMAN DAUM: Michael, I apologize. Let us hear from our industry representative, Dr. Decker.

DR. DECKER: In this case, the industry representative does have a specific comment, which

is although I was overseas at the time of the last meeting on this, if I recall my briefing materials and reports correctly, there was a vote on efficacy of this product at the last committee meeting, and it prevailed for all of the age groups, for the 50 to 64 age group, among others. Am I right?

Could I ask FDA to comment? Was the issue of 50 to 64, was that age group included in a prior vote of this committee on this product?

DR. MINK: That was not. The vote from the previous VRBPAC was across the ages.

DR. DECKER: All ages.

DR. MINK: For adults.

DR. DECKER: Right.

DR. MINK: It was 18 to 64.

DR. DECKER: Right, and 50 to 64 is a subset of that.

DR. MINK: And the 50 to 64 data was presented briefly by Dr. Nichol at that time, but the subset comparison had not yet been submitted to the agency. So this is the first time that these data, though it's a post hoc analysis, it's the first time these data have been presented to you.

DR. DECKER: Okay. So it's a murky issue. The point that I'm trying to raise though is

that I think one thing. There's a couple of unfortunate things in the data in the presentation here. One, of course, is that in retrospect I think many people wish it was an efficacy trial and not an effectiveness trial, although effectiveness ought to be adequate.

The second thing is that I think the sponsor suffered a little from the effectiveness trial in that I suspect because of the ancillary measures all being consistently in favor of effectiveness, there's probably not biological meaning to the absence of demonstration of reduction in illness, but yet they're saddled with that outcome, which is unfortunate.

But then the third thing is procedural. In essence, they thought already home free on efficacy in 18 to 64 and here it is addressed again and they're shot down on 50 to 64. I think having been at this committee for a couple of years, my experience is that sometimes we don't always honor our prior decisions.

I don't know if this exactly fits that, but I thought it was worth mentioning.

DR. MYERS: The question that was framed at the --

CHAIRMAN DAUM: Are you going to -- tell me what you're going to do.

DR. MYERS: I was going to just comment.

CHAIRMAN DAUM: Please go ahead. I'd like to announce the vote as soon as you -- go ahead and make your comment.

DR. MYERS: I was just going to say you weren't at the last meeting, but the question as formulated did not include the breakdown of the subgroups. It was 16 to 64, not broken down the way it is.

CHAIRMAN DAUM: Okay. Thank you, Dr. Myers.

The committee had voted, and the issue of efficacy for ages five to 17 years, 14 members in favor, four opposed.

For the issue of efficacy in 18 to 49 year old folks, 17 members in favor, one opposed.

For the issue of efficacy in 50 to 64 year old folks, four members in favor, 14 opposed.

And that concludes our deliberation on question two. I'd like to move on now to discussion point three. I suspect that the agency has already heard many of the issues that we would raise vis-a-vis question three, discussion point three. This is

not a voting question. So we can have some free discussion about this if people wish or we could just ask people to comment on this question.

If anyone wishes to open the discussion. Dr. Katz.

DR. KATZ: I don't want to open the discussion. I want to ask a question of the FDA, and that is: what is done each year with the inactivated vaccine when new strains are incorporated into the vaccine for that year? Are there human trials done? And if so, what's their magnitude?

DR. LEVANDOWSKI: No, there are no human trials that are done for inactivated vaccine each year, but the purpose for this study is somewhat different in that it's looking at a safety parameter of a new live virus.

DR. KATZ: I wasn't asking for justification, Roland. I was just asking for the record.

So for the record, there are no trials done with the new vaccines.

CHAIRMAN DAUM: Okay. Dr. Edwards and Dr. Decker.

DR. DECKER: Wait a minute. Can I

clarify that? Because that's not correct. There are no trials required. They are done. There are trials done every year.

The FDA is not one of the licensing bodies that requires those results. Other licensing bodies elsewhere in the world do require them, and the trials are done.

CHAIRMAN DAUM: Can in about 30 seconds you tell us a little about those trials?

DR. DECKER: Virtually identical to what's proposed for this.

CHAIRMAN DAUM: Thank you.

Dr. Edwards.

DR. EDWARDS: I think one of the interesting features about the cold adapted vaccine is that in certain years the H1N1 may look more immunogenic than in other years, and the same with the H3N2. So that I think that at least in our trial, which is not FluMist, but is from the same mother or father, and preferably mother, that you would notice that there may be some need to look at the intrinsic immunogenicity of each strain because there is some difference.

And so I wonder if that should be something that would be asked more routinely than

with the inactivated because with the inactivated the immune response is pretty much comparable each year, in that same ball park, but that may not be the case.

I mean, certainly with Dr. Belshe's studies, the H1N1 strain was less immunogenic, and in our studies the H1N1 was more immunogenic. So there may be intrinsic differences when you give a different code to the same virus.

CHAIRMAN DAUM: Thank you.

Other comments about discussion point three? Dr. Stephens, would you care to offer any comments about this?

DR. STEPHENS: Well, I'm in agreement that the studies as proposed should be done. I think that without question they should be done given some of the safety concerns that were mentioned.

It would also be nice, going to Dr. Katz's repeated comments, to obtain some additional immunological data on the new reformulated vaccine each year as a correlate, obviously appreciating that the surrogate of protection isn't fully, but I think more immunological data and more testing in animal models is also something that I would

suggest.

CHAIRMAN DAUM: Thank you.

Dr. Snider?

DR. SNIDER: I had a similar question in looking at the annual clinical release testing that was the data we were shown and the indication that it demonstrated the feasibility of annual testing.

The question of, you know, what endpoints might be useful that could be gathered really rather quickly that would be of utility to the manufacturer, FDA, and all of us involved raises the question of whether we could get some serological data, and so I guess I would ask Nancy or Roland or someone who is more familiar with this if that would be a problem or something that would be doable.

CHAIRMAN DAUM: Dr. Cox or Dr. Levandowski, do you want to comment on Dr. Snider's idea?

DR. COX: Well, I think it's a good idea, and it certainly is doable. So that's something that's desired.

DR. SNIDER: I would concur and recommend it, and since it seems feasible.

CHAIRMAN DAUM: Roland?

DR. LEVANDOWSKI: Well, I actually was having another conversation while you were making your comments. So I'm not quite sure I got it all, but if the question was, you know, why not collect information on the immunogenicity of the vaccine at the same time, of course, that could be done. It just adds another parameter of difficulty in getting things done in a fairly quick period of time.

I think everybody is aware that for influenza vaccines to be useful they have to be available, and part of the point of doing this study, as I mentioned, is really looking at safety parameters for a new strain that might be incorporated into the vaccine.

That by itself takes some period of time to do just that clinical study, and although the information could be available at some point, it's likely that it would not be available at any time that you could use it for anything meaningful related to production of the new vaccine or what's going to happen with it.

I think it's a very similar situation that we find ourselves in with making inactivated vaccines where by the time they're available to do a clinical study, they really pretty much have to be

used.

So I think there are some logistical issues that would, although the information could be useful, ultimately would probably not be useful in a fashion that you would have it before the vaccine could be made.

CHAIRMAN DAUM: Dr. Diaz, this issue?

DR. DIAZ: Actually it's somewhat related to that. I was curious to the manufacturer's comments about the annual time frame. Every year we sit here, and we march through in getting to the next season's flu vaccine under a fairly tight time frame based upon making an inactivated influenza vaccine. I'm wondering how that time frame compares to what you have to go through or would have to go through with an annual cold adapted flu strain.

CHAIRMAN DAUM: Manufacturer like to speak to that? I think we've heard Dr. Levandowski on this point, but of course, he's welcome to say it again if he wishes.

DR. YOUNG: Yeah, I think if I understand your question correctly you're wondering in terms of when VRBPAC actually selects the strains for the upcoming season's vaccine do we actually

have enough time to make it --

DR. DIAZ: Right.

DR. YOUNG: -- and go through the process of --

DR. DIAZ: Exactly. I mean, Dr. Levandowski was addressing doing safety studies, but I'm just looking at the pure manufacturing aspects.

DR. YOUNG: Yes. I think, frankly, the issues are similar with either the inactivated vaccine or the cold adapted vaccine. We actually are already making cold adapted strains for the Brisbane, for instance, that has been identified in the southern hemisphere as a potential candidate for next season's vaccine. We try to stay ahead and obviously monitor the discussions of all the agencies around the world who are monitoring flu variability around the globe.

But in terms of once the actual strain is selected, if we haven't as yet started making that new master virus strain, it takes about four weeks to make that strain, and frankly, I think the inactivated vaccine manufacturers have to get a PR8 recombinant that grows in eggs well from the agencies. They make a reassortant for that wild type virus as well.

So I don't think that the timing is really that much different. The actual amount of manufacturing, the amount of eggs used, for instance, is quite a bit different for the inactivated vaccine compared to the cold adapted influenza vaccine because we actually rely on the nose to make a lot of the vaccine for us. So we put far less virus into the nose than you actually do when you inject it into the arm.

So the level of eggs that we need to make the same number of doses is probably ten to 100 times less.

CHAIRMAN DAUM: Thank you.

Dr. Hamilton, any comments on discussion point three?

DR. HAMILTON: It's already been stated.

CHAIRMAN DAUM: Good.

DR. HAMILTON: We're interested in efficacy data.

CHAIRMAN DAUM: Thank you very much.

Dr. Eickhoff.

DR. EICKHOFF: A comment. Only, again, the efficacy data, and that could be purely a subset of those 300 adults. Twenty-five or 30 individuals probably would suffice.

That's all I wish to say.

CHAIRMAN DAUM: Dr. Cox.

DR. MINK: Discussion point number three is about the committee's input for the design endpoints of the clinical study for release of new strains.

CHAIRMAN DAUM: Right. so it's not building on what you told us about questions one and two. It's anticipating, I guess, a world where this vaccine were on the market and being revised every year with new strains, and then what studies would you like to have on those new strains each year.

DR. MINK: Right.

CHAIRMAN DAUM: Do I have it right?

DR. MINK: And the study that was performed was a safety trial in adults using you saw about 330 or 300 or so adults. So the next discussion point is about post marketing studies.

CHAIRMAN DAUM: Thank you.

Is that clear or are people still mystified by that?

DR. SNIDER: I'm still mystified.

CHAIRMAN DAUM: Mystified. Okay. Check in here, Dixie.

DR. SNIDER: Sam brought it up earlier, but I mean, I seem to hear something different from Nancy and Roland about the feasibility of doing some serological studies, and I seem to recall a few years ago we had a problem around some elderly patients with flu vaccine that didn't give us serological responses that we had hoped for in a nursing home, and so I'm confused at this point about the role of serological testing in terms of annual evaluation, as well as even its potential role in helping us sort out whether the 50 to 64 year olds are going to respond as well as younger adults.

So if someone could clarify for me a little bit more about serologies, I understand about serologies in general not necessarily having a surrogate marker, but I also seem to hear that there's some utility to it, especially in terms of relative responses in different age groups or from year to year.

So if I could get some clarification I'd appreciate it.

CHAIRMAN DAUM: Dr. Levandowski and Dr. Decker wanted to comment on this as well.

DR. LEVANDOWSKI: Okay. Well, I'm not

sure I'm going to clarify much, but I just wanted to comment on a couple of things. The study or the experience that Dr. Snider was referring to with the vaccine where there were low responses, I think you're referring to the vaccine that was the vaccine that was recalled in 1996, and the concern there was really that the vaccine itself was so potent. So there was an attempt made to identify whether there was a good antibody response in the recipients of that vaccine or not and whether a recommendation should be made to revaccinate.

That is a little bit different situation from, I think, what we're dealing with generally from year to year in terms of immunologic studies. We don't have a requirement for doing a clinical trial in the United States for inactivated vaccine, but we're glad to have studies done so that we can obtain sera from people who are being immunized with the most recent, current vaccines that aren't available until the fall each year when we can get those materials from a clinical trial.

We generally use that information to help us in trying to predict whether the current vaccines will produce antibody responses that will cross-react with the newer strains that are out

there. We're not really looking to compare the vaccines one to another, nor are we looking to compare what happens with the current vaccine with what happened in terms of immunogenicity with the previous year's vaccine because the trials, first of all, can't be probably big enough to do what we would need to do, and the funding certainly isn't there to do really massive kinds of studies.

But what we're generally trying to do every year with that information really is to help us with vaccine strain selection, and my comments earlier about timing. I think there could be information that could retrospectively or, you know, would be retrospective data by the time we got it. I don't think it would help us with the current vaccine, but could help in the long run with understanding immunologic responses from the attenuated vaccine, if that's what the intent of the questions and comments was earlier.

But I still don't know and others may want to comment whether that could be used in a prospective fashion to say anything about what the likelihood of live attenuated vaccine was having in terms of being immunogenic and effective. And I think we still don't have full understanding on what

the meaning of antibody responses from the live attenuated vaccine would be and only because there are multiple pathways by which the immune response may be the systemic antibodies, the local antibodies, secretory antibodies, and also probably some cell mediated responses that help in that.

I think we won't get the full facts from any one measurement on that, and it's something that needs to be done in a better way than just as part of a study that we're really trying to use to identify safety parameter for a new strain.

CHAIRMAN DAUM: Thank you, Roland.

Is this a very, very brief comment? Because we're really beginning to get some time pressure here.

DR. CONNOR: I just wanted to clarify the intent of the study just to make clear that the trial that we have done and are proposing to do is a safety release trial for the vaccine each year. So obviously as people pointed out, the goal is to get the vaccine tested and released quickly.

The other thing is that the adult population is probably not the best population to be looking at the immunogenic response and that we usually can't detect immune response in most of the

adult patients post vaccination.

So that would have to be done in a pediatric population or some other setting in some other venue, I guess, is my point.

CHAIRMAN DAUM: Thank you very much, Dr. Connor.

I would like to continue just polling the troops here and ask people to refocus themselves on discussion point three, which is the clinical studies that you would like to see done/required for the release of new strains.

And I think we left off with Dr. Cox next up. Maybe you've already said your piece.

DR. COX: I think that the study that was presented here is really adequate. We are holding the live attenuated vaccine to a higher standard than we do the new trivalent strains, and I think that that's appropriate, and that the proposal here is a good one.

CHAIRMAN DAUM: Can you just say in about six words which proposal you mean?

DR. COX: Where they looked on page 22, the FDA's slide set, there is a slide that talks about annual clinical release testing methods.

CHAIRMAN DAUM: Thank you.