to say specifically what more data you need a little bit later. So, thank you.

Dr. Katz, please.

MR. KATZ: I think my colleagues have already expressed a number of the caveats or the concerns. I think the other aspect, of course, is what one considers in the pragmatism of the implementation of recommendations. And I'm very persuaded by Dr. Steinhoff's reminder that even if it's one dose in the first year, you're going to get a dose every year after that; if indeed the recommendation becomes one for universal immunization. And that's another committee or another two committees and their distinctions.

I think that we do have in my judgment sufficient data to be very comfortable from 18 months of age up. And the 12 to 18 month I, too, would like to see additional data.

I'm very reassured by Dr. Mendelman's comment about the 2,000 youngsters who will be enrolled in the study of concomitant vaccines, MMR or given along with FluMist in the beginning of the second year of life. So I think those data are already beginning to accumulate.

I think that we forget sometimes that we

have other vaccines where we've targeted different numbers of doses, the most recent being pneumococcal conjugate vaccine where we recommend three in the first year of life and two in the second, and one thereafter. So, I don't think it's a new venture to think of different dosing. But I'm comfortable with one dose at all ages at this point, given the fact that you're going to pick up the others as you go along and the pragmatic aspects of how many visits people are going to make at different times.

I'm comfortable with the adult data, so I would vote yes, yes.

CHAIRMAN DAUM: And I thank you.

Dr. Schild?

DR. SCHILD: Thank you. I'm comfortable with the efficacy data. I would vote yes on both issues. However, with a strong recommendation for future work that effort is put into mapping the effect on efficacy of antigenic changes and genetic changes in the viruses. We have only limited information on that for the moment. And also the collection of data for immunological markers for protection.

The conventional wisdom for inactivated vaccines is that hemagglutination inhabitation titers of equal or greater than 40 relate to protection. And

that clearly is not the case for these vaccines. And it's going to important in terms of future developments in the use of these vaccines to get some much clearer information on markers for immunity.

Thank you.

CHAIRMAN DAUM: Thank you.

Dr. Cox?

DR. COX: Yes. That was not a vote.

I think that the efficacy data are really quite strong for FluMist vaccine. It would nice to have additional data in the youngest children. It would be nice to have additional data in adults, particularly in adults 50 to 64 years of age, but the data appeared to be quite solid.

So my answer to question one is yes. And to question two is yes.

I would like to make a comment about --

CHAIRMAN DAUM: 1(a) and 1(b), Dr. Cox. If I could just make sure we're on the same page?

DR. COX: Sorry. 1(a) and 1(b), yes, exactly. Sorry.

CHAIRMAN DAUM: Thanks.

DR. COX: 1(a) and 1(b).

With regard to the one dose versus two doses issue, I think that given what we know about

inherent differences in different strains to induce antibodies and what we know about different eras of circulation of H1 versus H3, I think two doses for the first vaccination of children would be appropriate to make sure that we maximize the antibody response. There's just a lot of data that would indicate that would be quite prudent.

With regard to the interval between doses, clearly we don't have quite as much data as might be nice, but I think 30 days is very reasonable. We've seen data for 30 day intervals that looks very good. And because we already have recommendations for the inactivated vaccine that requires two doses in children under 9, that recommendation would be consistent with what we are already doing in that age group.

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

Dr. Eickhoff?

DR. EICKHOFF: For 1(a) children age 1 through 17, I'm quite comfortable with the efficacy data and would certainly vote yes on that issue.

The question of dose, number of doses in children under nine, let's say, I believe for now I would vote to recommend two doses in children less

than nine years of age, recognizing that that may in a certain sense be overkill and subsequent data may, indeed, confirm that one dose is quite sufficient. But at least for the moment I would sort of go into the same recommendation that currently exists for the inactivated vaccine.

Question 1(b) I think I may be the minority report here, because I'm going to vote no on question 1(b) for the following reason. I have no doubt that FluMist will be indeed -- is indeed effective in healthy adults. The question in my mind is how effective.

This is also a population in which in the inactivated vaccine is quite effective and FluMist or the live attenuated product may, in fact, be inferior to the inactivated vaccine. I don't believe that's going to be the case, but I don't really see the data that would permit me to make that judgment.

So, that's the reason I'm going to vote no on 1(b).

Additional data I've talked about a little bit. The H1N1 challenge study is promising, but again I would be much more comfortable with more field trial efficacy data. And, of course, for adults who are other than healthy, a great deal of additional

information is necessary. But I think licensure is not being sought for such adults at this time.

CHAIRMAN DAUM: Thank you very much, Ted.

Marty, Dr. Myers, please?

DR. MYERS: Well, I'm gold that Dr. Edwards asked the question about the limitation of our responses being defined by the specific studies. It's very difficult to sometimes separate out the application studies from the others.

I find the data for the 15 month to 71 month very compelling, but I do not think there is sufficient efficacy data to make a recommendation for under 15 months of age. And I'm uncomfortable in the 15 to 24 month age group.

So, like Dr. Griffin, if the question is 1 to 17, my answer would be no. And if the question is 2 to 17, my answer would be yes. That's taking into account also that we do not have any data on concomitant administration of other vaccines, particularly the MRR and vaccine.

We have to extrapolate between 72 months and 17 years, because there is no direct efficacy data for that age group, but I'm comfortable doing that because of the established effectiveness both below and above that, although I'd like to see data for that

group.

I don't -- I'm unable to determine from these data about one versus two doses. I have a prejudice that we'll need two doses for younger children, but I can't tell where that cutoff is. And if you include data from other than those from the pivotal studies, I think it's likely that Dr. Katz is right, that the single dose will be sufficient. But from these data, I just -- I don't think there's sufficient data to be able to address that.

On question 1(b) even despite the fact that the nonspecific primary n point wasn't achieved, I think that the more specific n points establish efficacy. I really would like to see data for more seasons, however, than just the one.

And then I would, in addition to the data for concurrent schedule vaccines, I'd just like to express my concern about the real world impact of the cold chain on the application of the vaccine efficacy. It's a whole lot different outside of the study circumstances managing cold chain. And the data that was in the briefing book about the frost-free freezers I think is very worrisome and needs to be -- that needs to be addressed. Otherwise the efficacy will be far less than has been shown in the study.

And then finally, I have reservations, we've been asked to comment on travelers. I have reservations about the use of the vaccine in travels to areas where avian influenza exposure is likely for the reasons that we discussed yesterday.

I think we're going to talk about what other data we would like separately.

CHAIRMAN DAUM: Dr. Myers, before we leave you, on part 1(b) the adult population, I didn't get your vote.

DR. MYERS: Oh, I thought I'd said yes.

CHAIRMAN DAUM: Okay. I didn't catch that. Sorry.

Dr. Edwards?

DR. EDWARDS: I think almost all the wise things have been said, so I would like to comment on, first, the pediatric and adolescent population.

I think we do efficacy studies for a very clear reason in defined populations, and that is to determine what the efficacy is. So that I take the age of the pivotal efficacy study very seriously, and so I really think I can't comment or don't feel that there's adequate data between the 12 and 15 month, as a number of people have already said.

I do think there is adequate data from 15

months to 17 years to say that the vaccine will be efficacy for H3N2. I think it also will be efficacy for H1N1, but I don't think that the number or the quality of the challenge trials in either the pediatric or the adult population really affirms that.

I do think that previous experience and certainly previous experience that we've had would suggest that it will be efficacious. So I will say yes for the pediatric to adolescent 15 to 17 years.

I'm a little bit more concerns, as Dr. Eickhoff is, about the adult population in that I pondered some whether we've ever had an effectiveness trial to be used to license a vaccine, and I couldn't remember that we did. Perhaps I'm wrong.

I think that a standard for a trial such as this really is efficacy that is culture confirmed, although I agree that this is likely from -- that the reduction and the effectiveness we see is from a reduction in influenza. But I don't really want to start a precedent of really not looking at efficacy trials in the purest sense.

I do think that we don't have data about repeated dosing, particularly in adults. And I think the data that suggests that immunization of adults that have previously seen these wild type viruses, the

vaccine may be efficacious and I think whether it is as efficacious as the inactivated is not a question that we're asking, but I think is one that hasn't been answered.

I also don't feel -- I'm uncomfortable with the challenge data. It seems like there should have been a higher infectivity rate and we could have gotten a bit more information with larger numbers of individuals in those studies.

So, I will say yes for the adult population, but not with a very warm and cuddly feeling, because I don't think it's the most optimal way to get vaccine efficacy.

CHAIRMAN DAUM: And, Dr. Edwards, so we can record your preference properly. For the younger children you're --

DR. EDWARDS: Fifteen to 17, yes.

CHAIRMAN DAUM: Fifteen months to 17 years?

DR. EDWARDS: Yes. Yes. Right.

CHAIRMAN DAUM: So the answer to the question is no, but if the question were reposed to 15 months to 17 years, it would be yes.

DR. EDWARDS: That's correct. And then I also did want to comment on the two dose. I think,

again, as I mentioned before pivotal efficacy study we have to use the data that was gleaned from that, which is the two dose schedule. That's not to say that I think -- don't think that Dr. Glezen is totally right that we may just need a single dose, but I think that has to be shown.

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

Dr. Steinhoff, not least.

DR. STEINHOFF: Thanks. I can be brief, because I think many important comments have already been made.

1(a), the pediatric adolescent population, I have to agree with a lot of my colleagues that the questions as posed, 1 to 17 is difficult to say yes to. I don't think there is good efficacy data or substantial amount of efficacy data below the 15 months.

The issue of two doses, the efficacy data did not show that you needed two doses for good efficacy. And so I think that we need more data for the indication that's been applied for.

So my recommendation is to have more information about the two doses.

At what ages is it necessary for efficacy?

Part (b) --

CHAIRMAN DAUM: Could you finish with part (a) first? Are the data adequate to support the efficacy of FluMist in pediatric and adolescent population 1 to 17 years of age?

DR. STEINHOFF: I said above 15 months yes, but below no.

CHAIRMAN DAUM: Thank you. So it's no?

DR. STEINHOFF: Yes. And for (b), the adult population, I think the data for efficacy is adequate there. The additional information that everyone seems to have mentioned, and I agree with, is that the H1N1 information, so there should be a recommendation to perhaps design a challenge study to answer that specific question. That's a yes.

CHAIRMAN DAUM: Thank you very much.

And I guess that it's my turn. And I think since we last heard about this vaccine, that the progress has been marvelous. And I think that the efficacy data, particularly, are pretty persuasive. I think there's real reason to believe that this vaccine prevents influenza. We're not there yet, as my colleagues in the Committee pointed out with their comments. There are issues to be addressed.

I think Dr. Edwards' comments are most

persuasive, that the 15 month cutoff makes more sense given the available data. And I'm concerned mostly about the age chosen for the trial rather than the concern about the concurrent vaccines. I think data must be there regarding concurrent vaccines. But I guess my personal view is that that's unlikely to influence the efficacy.

So, I'm also persuaded that I haven't seen anything that really persuaded me that two doses was necessary. I must say, it's an interesting concept and it's one that could be developed more. But there was an improvement in the serology, to be sure, to one of the types but on the other hand, there really wasn't any change in efficacy that I could see. And I don't know what serology means.

I was struck by, to borrow a phrase from Ms. Fisher, "our lack of understanding of what the relationship is between immunogenicity and efficacy." So that remains an open question.

The H1N1 data, as everybody in the Committee has noted, a real world circulating virus would have been better. But I thought the challenge studies were pretty well done and convinced me that it was pretty likely that H1N1 efficacy was there.

If there were two doses, I don't know what

the optimal interval would be between the doses. I must say I saw very little information that persuaded me how to evaluate that critically, and I'm not sure I have a wise recommendation as to how that should be done.

And so, I guess I'm in the no for part 1(a), but if age were changed to 15 months, I would be in the yes.

And for the adult situation, this is efficacy. We're going to talk about safety a little bit later, I think the data are compelling that we saw, that this vaccine is efficacious in adults and I'm in the yes camp there.

I hear the concerns about the repeat dosing issue. We don't know much about that, year to year. And adults have lots of diseases that impair their ability to respond to vaccines, and we obviously need to know a great deal more about that than we do. But I believe that the efficacy part of this discussion is solid and a vote yes there.

And that concludes our vote on question one.

For question 1(a) I believe we have eight Committee members answering yes and seven answering no. Of the seven that answered no, five of them

qualified that by either saying 15 months or two years of age. If the question were rephrased that way, the answer would have been yes.

So you at one hand might say this is a very divided issue, but I think most of the controversy is in the youngest infant, 12 to 15 months or 12 to 23 months depending on which Committee member was speaking.

For the adults, question 1(b) in terms of efficacy, the vote was pretty strongly in favor of yes. Twelve in favor and two opposed.

We'll have a final check here and make sure that's right.

MS. CHERRY: I got 13.

CHAIRMAN DAUM: Thirteen. I forgot to count myself. Thirteen yes and two against.

So we're done with question one. And I thank the Committee, as always, for their very elegant careful discussion.

I want to go right on to question two. And Dr. Mink, I hope, is ready, will remind us what question two is.

I believe that the Committee can go through given the extensive discussion we've already had, discussion points 3 and 4 in a more rapid

fashion. And so I think the proper thing to do is question two up there, get that discussion started and make sure we get all the points flushed out that we want to raise there.

Thank you, Dr. Mink.

DR. MINK: Question two for the Committee is are the safety data adequate to support safety of FluMist in the population in which an indication is being sought (i.e., 1 to 64 years of age)?

Please discuss the adequately of the safety data in subjects less than 2 years of age, in the overall pediatric population, in adolescents, in adults and specifically in adults greater than or equal to 50 years of age.

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

And now my slides. The safety conclusions from FDA presentation yesterday were please remember this BLA is on a 10 month clock and was initially submitted to us in October 31, 2000. Much of our review is ongoing.

The review of respiratory events including pneumonia, bronchitis and others not yet discussed are not yet complete. A summary of these events have not

been presented in the BLA, and this review has primarily been performed by database searches.

Both the FluMist and normal allantoic fluid placebo were reactogenic in all age groups for which we've had data in the BLA which has made it more difficult in evaluating the reactogenicity of the FluMist.

Most safety data have been generated in healthy subjects. There is a risk of inadvertent exposure to individuals with underlying illness in the age group being sought, and we've seen a few high risk subjects presented in the briefing document, and there was a suggestion of increased in reactogenicity events for asthmatics.

For serious adverse events the CFR definitions of hospitalization, prolonged hospitalizations, death, congenial anomaly, cancers and overdose have been the primary criteria in searching for SAEs, as consistent with all studies in the CFR.

Some of the studies presented in the BLA did have active monitoring performed for all SAEs, and when it was performed it was for 28 to 42 days post-dosing.

There have been questions about an

increase in reactogenicity events seen with annual dosing of children. And the studies presented, AV006 in year one and year two and safety data in year three, there was no increase in REs noted.

There have been few subjects at the either ends of the age spectrum and in the database presented to you the number of subjects less than 24 months was approximately 1250, although we saw an increased size from Aviron this morning. And in subjects from 50 to 64.9 years of age, it was around 500 individuals.

Since we're going to do the additional concerns, additional concerns include concomitant immunization, and at this time we have no data for efficacy or safety with concomitant immunization. This included pediatric vaccines with additions of Prevnar, MMR, Varicella, DTAP, and I'm probably forgetting some, that can be used in the age group from 12 to 24 months especially.

There are also no concomitant immunizations with travelers' vaccine, which may include additional live viral vaccines or in any age group, including the use of CAIV with pneumococcal vaccine.

For transmissibility we've seen the preliminary data from the Finish trial in day care

where there was shedding of the CAIV strain in one of 99 placebo contacts.

And for annual vaccination, we have no data for revaccination in adults.

Any questions?

CHAIRMAN DAUM: No. Thank you very much for orienting us toward the task at hand.

I would now like to have some general committee discussion to clarify issues.

Thank you, Dr. Mink.

That you feel you want more information on a clarification on before we vote on question 2.

George, if you could do your thing and put question 2 back up there for us, I'd be grateful.

And, Dr. Kohl, we'll start off with you.

DR. KOHL: I have several major issues, at least in my mind, regarding safety. I believe we've heard about three separate studies regarding the possibility of pneumonia. In one of those studies there was an increased risk of pneumonia post-immunization, and I think that was the pivotal study or post-lower respiratory tract infection. And in two other studies, Paul Glezen's study and Steve Black's study, there was not increased risk.

I'm still somewhat concerned about that.

I don't want to see pneumonia lurking back there the way it did with rotorvirus. If there's any other data on that, I'd love to see it. That's number one.

Number two, I too felt that there was a hint of an increase reactogenicity in as asthmatics given that small study on pediatric asthmatics. I believe it was about 25 in each group where asthmatics who had an exacerbation of their disease received the FluMist and not the placebo. And although Paul Glezen said in his study there was no increased risk in asthmatics, I think he said that, I'd like to hear Steve Black in particular comment on that, because I presume there were a number of asthmatics immunized in the California study.

CHAIRMAN DAUM: Okay. Before we hear responses to those, I'd like to ask FDA folks, Drs. Mink or Geber or anyone else at the table, what is in the BLA with respect to the two issues that Dr. Kohl's asking about.

DR. MINK: There are no summarized data for pneumonia presented in the BLA. The data from AV006, as I've mentioned, was from our search of the database, inspection reports, line listings, SAE reports, anything that we could find. So, our relative risk calculations from AV006 are based on our

searches with the numbers that have been submitted.

For AV019 we have interim analysis which is not the same final total that Aviron was able to present.

And from AV012, we don't have that data. The only thing that's been submitted in the BLA for AV012 is year one SEA reports. We do have some line listings from parental reports which there could have been differential reporting because 80 percent of the subjects were in Scott & White HMO, but 20 percent were not. And so some of the line listing reports that we have seem to be from those line listings. So, it's differential. I don't know how much to emphasize that pneumonia is or is not a problem from AV012.

DR. GEBER: I think, too, what you're hearing from the FDA and what we're struggling with, and I think perhaps the committee is as well, is that we have received parcel study reports or study synopses for a number of the studies that are being discussed. And where we have completed study reports for the particular event that you're mentioning, pneumonia, that was not summarized for us. And so we've gone back to search the databases, and that's an ongoing process.

And so I think that's the difficulty, that

we can't come to you with our complete assessment of it at this point. And where we are is what we've presented to you. But that is where the confusion is.

We've received updates throughout the period of the review and we haven't --

DR. MINK: Nor have we completed the search for bronchitis and bronchiolitis, which could be coded differently based on age.

CHAIRMAN DAUM: So what I think we should do is to hear the data that bear on Dr. Kohl's very important questions, but to remember that given the fact that FDA wishes us to consider what's in the BLA, we may not wish or may not be able to get to full closure on question 2. And we'll have to do the best we can. But let's get the information out first and then we'll go from there.

Dr. Faggett, is this a procedural question?

DR. FAGGETT: Yes, it is. Just to look at the population in Temple, because that's a military town and I'm concerned who are the children? How many of them are military versus civilian, all that. Do you have a breakout on that?

DR. MINK: All I can tell you is that we

have the SEA reports and an ongoing study report for year one.

DR. FAGGETT: Okay. I'll withdraw my question, if they don't have the data.

DR. MINK: I can tell you the ages were from 18 months to 18 years.

DR. FAGGETT: Yes. My concern is follow-up because if it's a transient population, it could be a-

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DR. MINK: I understand.

DR. FAGGETT: Yes. Thanks.

CHAIRMAN DAUM: We're going to have to do some mental agility here, Dr. Faggett. Because I think the proper thing to do is to get all the information out that we can, and I want to do that. And so your question is a good one and an important one, but at the same time we're going to then have to sort of do some tethering in our minds because we're going to have to return to the question 2 as posed by the BLA data.

So, with that caveat, let's hear from Dr. Greenberg with regard to pneumonia and asthmatics. And, hopefully, he'll call on Drs. Black and Mendelman as appropriate to comment on those questions.

DR. GREENBERG: Thank you, Dr. Daum.

Pneumonia was raised yesterday and this morning as an area of analysis by the FDA. And as they noted, the analysis is ongoing. We plan to collaborate with them fully to help them complete the analysis.

And I think as part of that helping, I think that some data that Dr. Black present right now will be useful to the Committee, and if more is needed Dr. Mendelman can embroider that further.

DR. BLACK: I don't know how Paul's embroidery skills are, so we'll see what we can do here.

Yes, this was alluded to yesterday, but here it is in blue or black and white, I guess. The results from the final analysis data set in which there were 28 cases of pneumonia in the FluMist group and 17 in the placebo. This is all utilization settings in all doses and the entire age range.

The great rate ratio, as you can see here, is .82 and the p-value is .25. So there's not any suggestion of an increased risk of pneumonia here.

And if we go to the next slide, this shows you, again from the final analysis data set, where the cases of pneumonia occurred in the FluMist group in blue versus the, I guess, gray for the placebo. And,

again, you can see that they're is scattered throughout the time period.

In the next slide this breaks this down a little bit by different age groups, as you can see here, starting with 1 to 17 overall, which I've shown you, and then breaking it down into the younger age group again where there is not any suggestion. And if we go down further in age, 18 to 35 months or 12 to 17 months, again, the numbers get small but there's not any suggestion of increased risk here either.

CHAIRMAN DAUM: Thank you very much.

DR. BLACK: Do you want me to respond to asthma now as well?

CHAIRMAN DAUM: Yes, please.

DR. BLACK: With a little help here we'll try that.

We, in response to the initial signal that we saw in the data that we presented yesterday, which you can see is 6 cases in the FluMist group and zero in the placebo with a p-value that is significant for increased risk, went back and looked to see how many asthmatics there actually were in our population. And, as you'll see, I think we've demonstrated conclusively that querying parents as to history of asthma is not an especially efficient means of

excluding asthmatics from trial participation. What you can see here in all ages there's somewhat more than 800 children with a history of an asthma diagnoses by a physician in our databases in the period between January 1st of 1998 and their first dose of vaccine. So we've basically gone back on average about two years prior to first dose of vaccine and identified the subset of children who has a physician diagnoses of asthma in their record.

There are several reasons why the parents may not have been up front about the history of asthma, not the least of which is that there was -- they knew their children had been recommended in the past to get flu vaccine and last year there was really not any flu vaccine in our population until almost the end of the year.

And you can see here for dose one and dose two what we have. And this is for all ages for dose one or dose two. What we see is a rate ratio that's essentially one. And for dose two, again, the point estimate is a little higher, but there's not any suggestion of statistical significance.

DR. KOHL: Excuse me, Steve. What is that the rate of, that slide you're showing?

DR. BLACK: You want to go back?

DR. KOHL: What is that showing?

DR. BLACK: What this is, we took this denominator of children and then looked to see how many of them had a visit for asthma in the 42 day window following the receipt of the vaccine. So this is, in essence -- we have to be a little bit careful here because we're using the same outcome event as visits for asthma in the 42-day observation window, but we're using a different denominator. So this is not a confirmatory study. It's not a separate study, but it is a different way of, if you will, zeroing in on the question do children with asthma have an increased risk or not following FluMist vaccine of a visit for asthma.

CHAIRMAN DAUM: This tests parental recall then over previous history of asthma.

DR. BLACK: No. I don't know how -- no. No. Basically -- well, that may -- I don't know whether you're being cynical or not. But it does parental reliability, which I think in this case, as the question was to parents have you ever been told that your child has asthma. And if they said no, they were enrolled into the trial. And given the prevalence of asthma in our population, that questions eliminated perhaps a third of the asthmatics, but the

other two-thirds were not identified.

But in this age range there was not any suggestion -- in the overall age range, there was not a suggestion of increased risk. However, if we go to the next slide, again, if you remember the original association was in the younger children 18 to 35 months of age. And if we look here in clinic and also in the combined setting, you can see here these are the relative risks are either undefined or elevated. And there is a significant increased risk.

Now, again, I would caution you that the numerators here are largely the same as in the prior result. Remember, of the six children that we saw before, four of them had a prior history of asthma. So four of them are contributing to this data. And given the high proportion that had a history of asthma before, you would almost anticipate these results. But this answers that question more directly and I thought would inform the Committee.

CHAIRMAN DAUM: Thank you, I guess.

Okay. Dr. Eickhoff, Dr. Myers, other issues.

DR. GREENBERG: Dr. Daum, did you want additional data on Texas in pneumonia?

CHAIRMAN DAUM: With regard to pneumonia

or asthma?

DR. GREENBERG: Which?

DR. BLACK: Both.

CHAIRMAN DAUM: Yes. Can you hold on a minute, Dr. Eickhoff and Myers.

DR. EICKHOFF: This was a question for Steve Black.

CHAIRMAN DAUM: Okay. Let's see the Texas data first and then we'll go to that.

DR. GREENBERG: Why don't we ask Steve his question while we're waiting to pull up that data.

CHAIRMAN DAUM: That's a good idea. Dr. Eickhoff?

DR. EICKHOFF: Thank you.

Dr. Black, the pneumonia rates that you showed in that very first slide, do you have an idea what comparable rates would be for children in the same general age group absent any inhaled FluMist or inhaled placebo?

DR. BLACK: Given the timing of this study and the age range of this study, normally we would compare this to other studies and I could answer your question. But the follow-up period here is exclusively during the respiratory virus season and the age ranges and given the age distribution and the

sensitivity of the results to that, that's an answerable question, but I can't answer it right now.

CHAIRMAN DAUM: Are we ready or do we see what Dr. Myers wants?

DR. MENDELMAN: This is a summary from the AV012 Texas Community Prevention Trial. Medically attended acute respiratory illness based on the Scott & White data tapes, there are over 2000 subjects in year one and 2500 in year two.

The relative risk shown here, so with any medically attended acute respiratory illness, which includes URI, sinusitis and LRI, there's no increased relative risk.

And then the lower respiratory illness, which includes pneumonia, group, bronchiolitis, etcetera, there's actually a decrease. But again the point estimate is no difference.

In the subset on the next slide of children enrolled in study 12 who by parent history or RC09 code were identified with wheezing elements or asthma is shown on this slide.

These are the days zero to 14 period. Again, you've heard about compared to the reference period the same child being their own control from day 15 on and days prior to vaccination in the data tape.

Looking at medically attended acute respiratory illness, relative risk of 1.1, so there's no difference. And lower respiratory illness in this subset of children I should point out 326 in year one, 502 of these children in year two. .7 and .8 reduced risk but no difference. And in asthma wheezing reduced and no difference.

DR. GRIFFIN: Can you tell me just what the age of these children is?

DR. MENDELMAN: I'm sorry?

DR. GRIFFIN: The age range for this?

DR. MENDELMAN: These children are 18 months to 18 years of age.

DR. FAGGETT: Okay. Are those the same children in year one and two? Is that additional children for year two?

DR. MENDELMAN: These are additional children in year one, year two.

DR. FAGGETT: So that the 502 would be different children?

DR. MENDELMAN: Yes.

CHAIRMAN DAUM: Dr. Myers, is your issue about this issue, this very thing, or are you going to start --

DR. MYERS: It's related to the Houston

data, but it's a separate question.

CHAIRMAN DAUM: Okay. Let's hear from Dr. Goldberg. Is yours about this very thing? Let's hear that first and then Dr. Myers.

DR. GOLDBERG: Just one clarification on this slide. The reference period is the 15 day period pre-vaccination? Is that what you said? I'm sorry, I missed it and it's relevant to --

DR. MENDELMAN: It's a good question. The reference period in year one starts on the data -- any child being dosed, which is August 17th of '98 and ran through January 2nd of '99. And then for that individual child who was dosed, the 14 day period after their dosing to the time before they were dosed in those dates all the way through to January 2nd, 1999.

In year two the dosing started in September, so it's September 13th of '99 through January 13th of 2000. And it's presented in person-months.

DR. GOLDBERG: Just a question, though. If the child was vaccinated early in that period, so their reference period would be extremely short. So therefore you would have a bias against -- like if a child was having asthma or wheezing in like a two week

period right before, they might not be coming in for a vaccination at that point. So that there's a possibility that you've got some funny population --

DR. MENDELMAN: Well, the vaccinations --

DR. GOLDBERG: Or am I not understanding your data?

DR. MENDELMAN: Yes, the vaccination in both years of the trial ended in December. So going through to January would have collected the additional data.

DR. GOLDBERG: That's the post-data.

DR. MENDELMAN: Sorry?

DR. GOLDBERG: That's post-vaccination data. I'm talking about your pre-vaccination period that you're comparing to. Like for a given child, it could be relatively short or up to almost as long as that whole period?

DR. MENDELMAN: Right, most of that would be in the post-vaccination period. That's correct.

DR. GOLDBERG: All right. Thanks.

CHAIRMAN DAUM: Thank you.

Dr. Myers?

DR. MENDELMAN: Bob, could Dr. Glezen comment on this?

DR. GLEZEN: I'd like to clarify that. Of

course, if the child only got vaccine on the first day of vaccine administration, we wouldn't have any pre-vaccine period. But if the child got vaccinated two months later, we had all their clinical data starting with the first day of vaccination.

So there was no bias that you referred to there, as far as the data goes.

DR. GOLDBERG: I'm still confused then by your answer. You're saying your post data is within two weeks after vaccination. So are you saying the reference period includes then stuff after the 14th day post-vaccination as well?

DR. GLEZEN: That's right, yes.

DR. GOLDBERG: So it's a pre and a post?

DR. GLEZEN: Pre and a post.

DR. GOLDBERG: Okay. That was totally unclear.

DR. GLEZEN: Yes. Yes. Yes. So we have the clinical data for the whole period, our vaccine period which would be the day one the first period got vaccine to 42 days after the last person got vaccine.

DR. GOLDBERG: But is there implicit -- just let me make sure I understand this.

Is implicit in this then that a post-vaccination event is only within those two weeks.

DR. GLEZEN: Right. Right.

DR. GOLDBERG: Supposing there was a longer term relationship with some of these outcomes then, that would be being called their reference period, is that right?

DR. GLEZEN: This data refers to events that occurred zero to 14 days. However, we did look at all events over the entire period to see if there was any clustering, and we did not see any. There was random distribution of events throughout that period of observation.

DR. GOLDBERG: Okay. Thank you.

DR. GLEZEN: And one other point I wanted to make. The year two data did include some kids who'd had their second dose and kids that had just their first dose. It was about half and half. And we've looked at the same parameters in kids who got their second dose versus those that got their first, and there's no difference.

DR. GOLDBERG: Thank you.

CHAIRMAN DAUM: Dr. Myers?

DR. MYERS: We heard yesterday that obtaining cultures during the first part of the study period, I think it's the first ten days, was discouraged. And I presume that's because of --

CHAIRMAN DAUM: Before 14, I believe.

DR. MYERS: First fourteen. That's because of expected vaccine shedding. But we also heard a suggestion that those children had a clustering of influenza-like illness and 16 of the 17 positive cultures came from Houston.

So I guess the question I have is there's 16 cultures that were positive in Houston, what's the denominator of the number of cultures that were obtained and could we see the data for the culture positive versus the culture negative, what the symptom clusters were for those children?

CHAIRMAN DAUM: Thank you. Who wants to take this question on? Harry?

DR. GREENBERG: Paul, the question is about the Houston cultures, and here we are. Would you like to come up?

There are a couple of responses to this. Paul, why don't you start out?

DR. MENDELMAN: We presented this slide yesterday, and I guess you can't see it any better today. But -- sorry. We made a lot of slides last night. We didn't redo this one.

The randomized comparison for the 116 children who were cultured in 14 days after dosing in

study AV006 are shown on this slide. So this is the randomized comparison. There's 78 FluMist recipients and 38 placebo recipients. And then just moving down the events, the symptom complexes that CBER requested that we provided were if they had any of the three reactogenicity events, 48 percent of these FluMist recipients and 50 percent of the placebo recipients had at least three events on one day.

Looking at another definition of temperature greater than 100 degrees, cough with runny nose or nasal congestion, 9.1 percent in the FluMist, 7.9 percent in the placebo group.

And the CDC-ILI definition 19.5 percent in the FluMist and 21.1 percent in the placebo group.

And then these are the actual event that these events were complexed from. And maybe you can't see, I'll just read them.

The runny nose, 79.2, 71.1. Sore throat 27 percent versus 18 percent. Irritability 36 percent versus 47 percent. Headache 14 percent versus 7.9. Chills 11.7 versus 10.5. Muscle aches 10.4 versus 5.3. And decreased activity 31 percent versus 13.2. And temperature greater than 100 33.8 versus 23.7 and a higher set point of 102 7.8 versus 7.9.

Now, in the data presented also to you

yesterday was the culture positives for children who were sick who got cultured compared to the culture negative FluMist recipients who also were sick, but their cultures didn't happen to be positive. And I think it becomes a statistical as well as a clinical issue. And if Dr. Wittes could comment on the statistical, I think that might help.

Thank you.

DR. WITTES: And I even have a voice today, not my usual voice but one better before.

I think what you saw yesterday was a split. The FDA's presentation took the FluMist and split it into two groups; those who had positive shedding and those who had negative, and that was the nature of the comparison you saw.

That comparison, of course, is inherently problematic because it doesn't compare the two randomized groups, which is the FluMist versus placebo. And there's no way that you can identify within the group -- if you look at that placebo column, there's no way of being able to tell who in the placebo group would have shed had they been given the vaccine. So there's a selection problem in the comparison, I believe in the comparison that you saw yesterday.

Any variable that is confounded -- that's related to both shedding and to the symptoms will get confounded in the split that you saw yesterday. So we think you need to look at the two groups as they were randomized.

CHAIRMAN DAUM: Thank you very much.

I'd like to hear from Dr. Mink on this issue as well, and then we'll call on Dr. Edwards.

DR. MINK: Okay. I can try to answer both of your questions with our perspective, Dr. Myers.

First we mentioned there was this many cultures -- there were 17 FluMist recipients who had 18 positive cultures. 16 of those 17 subjects were from Houston. Culturing was discouraged in the first 11 days of the protocol. After 11 days it became part of the efficacy surveillance.

And kids who had illness, there were illness criteria stated in the protocol to bring them in for evaluation for cultures.

So these 16 kids at Houston in the first-- it actually turns out to be the first 11 days were brought in for culturing.

So we looked at the total number of cultures obtained at Houston. 31 out of 144 FluMist recipients were brought in. Of those 31, 16 were

culture positive. 31 who were ill FluMist recipients at Houston.

There were also 13 ill placebo recipients at Houston. So the culturing rate between the groups was about the same percentage.

We presented the data to you like this, acknowledging the statistical possibility of confounding. We weren't looking to compare FluMist and placebo. We were looking to compare who was ill that grew cold-adapted virus and who was ill that could have grown something else.

As Dr. Mendelman mentioned yesterday, I think it was -- you don't have data for what the other kids may have grown.

To be complete, we presented the placebo data. 36 of 38 subjects were negative. Two are coded in our database as other, but we presumed that's negative for CAIV. These kids shouldn't be shedding CAIV theoretically because they weren't given CAIV.

So in looking at who was ill and of those ill people who shed virus and who didn't shed CAIV and what their illness profiles. Okay?

Of these kids who were ill with shedding virus, 70 percent of them had at least three RE events on the same day. 41 percent of them compared to 13

percent of them met CDC influenza-like illness criteria. 100 percent of them had runny nose. And 70.6 percent of them had a 1.6 fever or greater. We have not performed statistical comparisons on these. These are just to present to you the illness profiles of these subjects.

With help from Aviron in gathering the data and this analysis is also ongoing, we present the negative subjects and the placebo subjects, and you can see that they're fairly comparable for those who didn't grow a cold-adapted viral strain.

Dr. Greenberg, did you want --

CHAIRMAN DAUM: Thank you very much.

Other Committee comment. Dr. Edwards is first.

DR. EDWARDS: I wanted to ask whether those samples may have been saved and whether those samples from all the vaccine recipients and the placebos might be looked at for RSV or PCRed for RSV, because I think it would be helpful?

DR. MENDELMAN: The simple answer is, Dr. Edwards, that all 5,000 cultures taken across both years of the trial are in the freezer.

DR. EDWARDS: So you can answer that from the original nasal sample?

DR. MENDELMAN: Correct.

CHAIRMAN DAUM: Dr. Edwards, can I flush you out a little bit out that, though? I think it's a very important point.

It seems like some children who get this vaccine may get a flu-like illness. And I agree -- are you suggesting that maybe it wasn't and it was confounded by some other virus circulating?

DR. EDWARDS: Well, I think if you do cultures on patients who have been given cold-adapted vaccine, you're going to grow cold-adapted vaccine. And I think what's confounding this issue, particularly as it relates to pneumonia, is that for those of us who do these flu studies or have in the past, you get the vaccine late, you're hurrying to get all these kids immunized before flu comes. And, unfortunately, RS comes before flu comes. So you have co-circulating viruses. And I think it would be helpful to shed if is there a pneumonia problem from cold-adapted vaccine?

I mean, there are going to be kids who have reactions to -- I mean, who have runny nose and some low grade fever from the cold-adapted vaccine. But the issue of whether we have lower tract disease I think is a very important one. And I really think

that it's incumbent that those samples be gotten out and PCRed to find out if there is a component of pneumonia, it may very well be RSV and not flu.

DR. MINK: I'd like to answer. The study AV006 was initiated in August and enrollment was completed in November. The Houston site, it's my understanding and recollection, was primarily done at the end of October and early November. So it was a little bit later than some of the other study sites. But most of the 14 day or 11 day post-vaccination would have been completed for those kids, I would presume, by the end of November at the very latest.

DR. EDWARDS: Could we have a comment from Houston about when the RSV season was then? I mean, do you remember that or -- I mean, I think it's basically kind of relevant, though, because I think one big problem is our discomfort with the pneumonia issue.

DR. GREENBERG: Bob?

CHAIRMAN DAUM: We want to deal with this question.

DR. GLEZEN: Okay.

CHAIRMAN DAUM: Dr. Glezen, are you able?

DR. GLEZEN: I can just speak in general terms about this. Tony Piedra was the PI of the

Houston contribution to this, and I don't have any of the data.

I can tell you that RSV virus isolated in Houston every month of the year. And the epidemics have been occurring earlier and have been very severe. This past year was the lightest year that we've had in quite a while. But we have surveillance data from Texas Children's Hospital, does a lot of antigenic detection.

So RS is definitely regularly present in August. And in October it's going to be very active.

Parainfluenza, of course, is every other year, whatever. But we also see parainfluenza at the same time.

And my recollection is that there are other viruses isolated from these same specimens, but I don't have the data. So we need to dig that up.

CHAIRMAN DAUM: Okay. It's getting close to lunchtime.

Harry, did you want to speak to this issue?

DR. GREENBERG: The pneumonia issue, which I think Kathy Edwards absolutely and Aviron takes very seriously, I just want to clarify in my own mind. We take great comfort in this very randomized placebo

controlled data that Dr. Black just presented to you and the very clear temporal data that he presented showing that both in the FluMist recipients and in the placebo mist recipients pneumonia did not cluster in anyway temporally. It was equally matched and occurred throughout the period giving no indication in a very large trial that pneumonia was not an issue.

I may have totally missed the boat here. I don't think Dr. Mink is talking about pneumonia.

DR. MINK: The 16 subjects in Houston, I just presented the influenza-like illness profiles of them. There was some subject who had pneumonia who was associated with a positive culture, but only that one subject for pneumonia out of those 16. So I can't make a comment about pneumonia other than that.

CHAIRMAN DAUM: Thank you.

I'd like to at this moment call on Dr. Goldberg for a final comment. Question about this very issue.

DR. GOLDBERG: Not about this issue. Something else.

CHAIRMAN DAUM: Can you hold it then? What I'd like to do is take a lunch break at this time. 50 minutes in duration and reassemble at 1:05 here and finish this safety discussion. And Dr.

Goldberg we'll start with your comment.

(Whereupon, at 12:17 p.m. the Committee adjourned to reconvene this same day at 1:14 p.m.)

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

1:14 p.m.

CHAIRMAN DAUM: Today is an airplane day, so we're most anxious to get started, lest we not be able to finish.

There are a couple of housekeeping issues or leftovers from this morning.

The first one is to reiterate the Committee vote on question 1(a). The vote was 8 yes and 7 no. Of the 7 no, 5 qualified their no. Two individuals said they would have voted yes if the question were phrased from 2 to 17 years. And three more individuals would have said yes if the question were phrased from 15 months to 17 years. So that is the correct and checked vote.

On the question 1(b) 13 Committee members voted yes and 2 voted no, and there were not

qualifications in that regard on that issue.

So I hope that's helpful and clarifies one thing that people seen confused about.

A second thing people seemed confused about were the data regarding asthma. And I'd like to call on Dr. Black to just literally take less than 2 minutes, as he's promised, and try and explain to us what I at least misunderstood this morning, and maybe others did as well. Dr. Black?

DR. BLACK: Okay. I apologize, but I'll try again.

Basically these are the original results that we had with 6 cases in the FluMist group and zero on the placebo group in the initial and then interim analysis dataset.

Next slide, please. What we did then is to go back and look using the entire dataset and asked a different question. The original question was for all children in the study how many had a visit for asthma in the FluMist group as compared with the placebo group. The question we then tried to ask is of the children who had a prior diagnoses of asthma in the population, which is a subset of the total population, how many of those had a visit for asthma following receipt of vaccine. And to do that we went

back to January 1st of 1998 to the first dose for each child and looked in their electronic medical record and asked did a doctor assign a diagnoses of asthma to this child either in the clinic, the ER or the hospital.

In so doing we identified, as you can see here, 852 children out of the total, about 8 percent or so, who actually had a prior-dose diagnoses of asthma in the population.

And then we then asked for those children what was the risk of a visit for asthma following receipt of FluMist vaccine for either dose one or dose two. And, as you can see, for dose one for example, the risk of a visit for asthma following receipt of FluMist was essentially equal for the placebo and the FluMist group. And for dose two the point estimate is 1.5, but again there was no statistically significant difference.

And on the next slide what we then did is go back to the original age group where we had initially identified this problem and again asked how many children had a prior diagnoses of asthma here and then subsequently had a visit for asthma following receipt of FluMist. And I guess the easiest thing to look at here, for example, in the clinic for both

doses combined you can see that the risk ratio was 3.8; that is children who had a prior history of asthma before receipt of FluMist were 3.8 times more likely to have a visit for asthma following receipt of FluMist than the controls. And that was statistically significant.

Is that clear?

CHAIRMAN DAUM: So can I try and rephrase it and see if it's to your liking? That you didn't intend to enroll any asthmatics in this study, but of those that managed to get in without you really realizing that they had asthma, there was a higher incidence of some kind of asthmatic episode among FluMist recipients?

DR. BLACK: Following receipt of vaccine for the 18 to 35 month olds. And we used a different ascertainment method here. For the entry into the trial we asked the parent. To determine this cohort, we actually looked at the electronic data.

CHAIRMAN DAUM: Thank you very much. That's extremely helpful and we'll take questions on this now. Dr. Edwards, Dr. Steinhoff, Dr. Katz?

DR. EDWARDS: Was that seen in any other age groups or you didn't do that because you didn't notice there was a difference in that age group --

DR. BLACK: Go back one side. I mean, if you look overall, we don't see anything.

DR. EDWARDS: Okay.

DR. BLACK: And you have to remember that the numerators are very similar to the numerators in the initial analysis, because it's the same 42 day window following receipt of vaccine. The only thing we saw, the initial elevated risk was, and it was in the 18 to 35 month old. And, in fact, some of the events that we're seeing here are the same events that we saw in the prior analysis. So it's not an independent collaboration of the initial observation, but basically it's answering a different question. And I wanted to make sure the Committee understood what that question was.

CHAIRMAN DAUM: Thank you so much, Steve.

Dr. Steinhoff, is it about this?

DR. STEINHOFF: Yes.

CHAIRMAN DAUM: Please.

DR. STEINHOFF: It's almost the same question that Kathy just asked. The original data you presented that this asthma association in your prospective study was only seen in this age group, correct?

DR. BLACK: Correct.

DR. STEINHOFF: And that's why you've done all these other analyses in that group?

DR. BLACK: Yes. And the reason we focused on this age group for this follow-up analysis is because that's where we saw the -- the only place we saw the observation in the initial analysis.

CHAIRMAN DAUM: Okay. And we have Dr. Katz.

MR. KATZ: In this notebook that we received in advance, pages 137 to 140, two studies are described in asthmatic children. 7.8.1.3 reactogenicity in participants with asthma. And, again, the numbers are small but what it says basically is that two out of 47 asthmatics who got FluMist allegedly had asthma, one out of 37 placebos allegedly had asthma.

And then the next study is again somewhat similar. And these are older children, I think, if I understand correctly. It says 9 to 17 years and 16 to 24 years.

Is this the right book, Nancy?

MS. CHERRY: No, I'm just looking at what page you're on.

MR. KATZ: I'm on pages 137, 138 and 139 and 140. The table numbers are 76, 77, 78. Yes,

that's it. And 75.

DR. BLACK: Bob, while they're looking for that, can I just comment on thing?

We have limited power to assess older ages because by the time the children get older, they're more likely to actually have the parent be aware that they actually do have asthma, and the numbers are smaller.

And also, the asthmatics that are here, although we can't verify this, I think are likely to be milder asthmatics. Because, again, if they were sicker I think that both the physician and the parents would be more aware of it as well.

MR. KATZ: In these tables I don't think they show what is written in the text, which is a very -- they're small numbers. But there are two with asthma in the FluMist, one in the placebo. And in the other study it's somewhat similar.

And I just wondered, are these the same children or are these different studies?

DR. MENDELMAN: These are children in -- I'm sorry, these are participants in Aviron trials. These are not participants in the Kaiser trial.

MR. KATZ: Okay.

DR. MENDELMAN: So study 10 was the study

in 9 to 17 year olds, 48 children with moderate to severe asthma based on the NHLBI guidelines. Randomized one to one doing a single dose of FluMist or placebo. And study 9 is the healthy working adult effectiveness trial where 36 of these adults got into the trial because their physicians didn't tell them they should get the flu shots they could be in a placebo controlled trial.

And you're right, in this group of 24 there were two exacerbations, that's 8 percent, within three days of getting FluMist. In this group there was zero out of 24. The sample size is limited, that's not statistically different, but those are the numbers. They were treated as outpatients.

In this group there were two exacerbations of 23, so that's about 10 percent. And there was one exacerbation of this 13 placebo recipients in AV009.

CHAIRMAN DAUM: Okay. Thank you very much.

I think Dr. Goldberg is first up with new items. So, before you start, I'd like to just ask Committee members to remind them that this is question 2, which has to do with safety. And so what we really want are people to pick out issues before we have the question that they need clarification on or want to

discuss, or just want to make a comment on. And we will do that.

Dr. Goldberg and then Dr. Cox and Kohl.

DR. GOLDBERG: Some data were presented on the contacts of FluMist vaccinated subjects, and I can't find them in my notes. Could you put that up again? There was a contact study that was described. Thank you. Pardon?

DR. GREENBERG: Are we talking about transmission study, is that correct?

DR. GOLDBERG: Yes. Yes. I didn't remember the number and I'm having trouble locating it.

DR. GOLDBERG: Yes. And you're asking about the slide that you saw?

DR. GOLDBERG: I'd like to see the slide that was shown yesterday. Thank you.

DR. GOLDBERG: It's Paul's primary. She asked to put it up again, the slide. Next slide.

Is this the one that you were looking for?

DR. GOLDBERG: There was a cross tabulation that you presented.

DR. GREENBERG: I'm blanking. This is the slide on the transmission study.

CHAIRMAN DAUM: Is this a time to have Dr.

Zamb get ready to show us the sequence of the shed virus, which I would like to see?

DR. GREENBERG: I think what Dr. Zamb can do is actually, to save time, is to tell you the results very quickly.

CHAIRMAN DAUM: Outstanding.

DR. GREENBERG: Using words.

CHAIRMAN DAUM: Words are good.

DR. ZAMB: Good afternoon. My name is Tim Zamb, I'm from Viral Vaccines Research of Wyeth Lederle Vaccines.

I have spent a fair bit of time looking at the genetic stability of FluMist by doing extensive genome sequencing analysis. And we focused on the trial that the slide was just presented with respect to the Finish horizontal transmission study that was conducted in the 1999/2000 flu season.

CHAIRMAN DAUM: Could you take a minute, Dr. Zamb, and just raise the microphone so we're sure we don't miss your words.

DR. ZAMB: So what in fact we did was to evaluate the genetic stability of these vaccines following administration to individuals in this study. And we used three criteria in order to select them.

One was, in fact, based on the evaluations

and the Finish clinical lab with respect to the presence of influenza virus in the samples. This was done by standard virologic culture.

The second criterion we used was that we attempted to look at those that appeared to be single virus, vaxima virus rather than mixtures simply to allow us to do sequencing much more efficiently.

And the third is that we were looking for optimized or maximize the potential effect of finding misincorporations. So what we did was to tend to take samples that occurred later after vaccination than earlier.

We attempted to sequence 60 independent genomes with respect to having 20 genome representatives for each of the vaxima viruses that were present in the trial in formulation. That's the A/Sydney, A/Beijing and B/Harbin-like virus. And, in fact, we did see, as we would expect a few nucleotide misincorporations in some of these viruses. We saw misincorporations that ranged from zero to 6 per genome with an average of two misincorporations per genome.

With respect to that potential transmission case, we in fact did sequence that virus and found, again, three nucleotide misincorporations

in that vaccine virus that was recovered from the placebo recipient.

An identical pattern of misincorporation was found in a vaccinal virus from a vaccinee that shed that virus 5 day previously to the potential transmitter -- the vaccinal virus was shed on the 25th of February, the placebo recipient shed that same marked virus on the 1st of March, separating those two events by five days.

CHAIRMAN DAUM: And you conclude from that?

DR. ZAMB: That the transmission is a likely event and that that B virus was transmitted from that one patient, one subject, that was in the vaccine group and transmitted to one of the placebo recipients. However, I must state that all of this analysis was done on culture amplified virus. In fact, what happened i the Finland in the clinical lab was that the swabs were taken and amplified in an MDCK cells. Those amplified products were then sent to Aviron for further subtyping, and we received those amplification products for sequencing from them.

CHAIRMAN DAUM: Thank you very much. Are those data in the BLA?

DR. ZAMB: No, they're not. These are

recent data. We're generating them now and we're not finished with our analysis.

CHAIRMAN DAUM: Thank you.

Dr. Cox?

DR. ZAMB: One additional key point is that --

CHAIRMAN DAUM: Please be brief.

DR. ZAMB: Sure thing.

One additional key point is that the phenotypes of all these viruses were as expected, cold-adapted and temperature sensitive.

In addition, any of the misincorporations that were found in these clinical isolates were not associated with those loci thought to be the cause of the cold-adapted attenuation and temperature sensitive phenotypes.

In addition, that there was no increased pathogenicity associated with any of these viruses in the children that shed them.

CHAIRMAN DAUM: Pass received. Dr. Cox?

DR. COX: Most of my questions with regard to that particular instance have been answered now.

I guess the only additional question would be how many of the three nucleotide changes were also coding changes?

DR. ZAMB: They were all coding changes.

DR. COX: All coding changes?

DR. ZAMB: Yes.

DR. COX: Okay. And do I understand it correctly that that virus was put back into ferrets and determined to be attenuated?

DR. ZAMB: No, they weren't. They were cold-adapted and temperature sensitive.

DR. COX: In tissue culture?

DR. ZAMB: That's correct.

DR. COX: Okay.

DR. ZAMB: And the child who shed that virus did not express any unexpected symptoms. So it's apparently -- I mean, its attenuated phenotype is apparently maintained in the individual who shed that virus.

DR. MURPHY: Do you have serological data?

DR. ZAMB: There weren't any --

CHAIRMAN DAUM: Excuse me. I didn't recognize the speaker. Who spoke? No, I'm sorry, Dr. Murphy. We can't do that.

Thank you very much, Dr. Zamb.

DR. ZAMB: Sure.

CHAIRMAN DAUM: Dr. Kohl, please?

DR. KOHL: I could ask Dr. Murphy's

question, couldn't I? Do we have any serology data?

CHAIRMAN DAUM: That would be nice.

DR. KOHL: That'll be 5 bucks, Dr. Murphy. That's a joke, for the record.

So, my first question was was there any serology on those patients. And the second question was does Dr. Black have temporal data on the patients with the asthmatic exacerbations?

DR. ZAMB: With respect to the Finish trial, there weren't any blood samples taken. It's rather difficult in Europe now to conduct a clinical trial, especially on children that requires blood sampling.

CHAIRMAN DAUM: Second question.

DR. GREENBERG: We do and we are calling it up.

CHAIRMAN DAUM: George has a lot of helpers in the afternoon.

DR. GREENBERG: George has a lot of slides.

CHAIRMAN DAUM: While he's calling it up, I'll say that I marvel at the dexterity with which both FDA and sponsor have been able to produce data on demand having no idea what question we're going to ask next. And so we thank you for that. It makes the

discussion of high quality.

DR. BLACK: Yes. It's actually a shame you said that, because we don't have a graph. What we have, this is the graph that I showed you before on the initial data set of the six children who did have asthma following receipt of vaccine. We've not graphed the other children from the other analysis. We could, but we have not yet.

CHAIRMAN DAUM: Thank you very much.

Dr. Kohl, are you all set? Okay. I have you here.

Other Committee discussion? Dr. Edwards and Dr. Stephens, Dr. Schild.

DR. EDWARDS: I did want to just go back to the slide number 70 from the FDA yesterday where there appeared a line listing of pediatric pneumonia cases. And granted, this is still a work in progress, but I wondered if there was a possibility to shed any additional light on any of those cases or to give us a frame of reference to compare this study 006 and the one 009 in terms of relative risks of pneumonia. Because I think this is an issue that I'm sort of grappling with. Do we have adequate data that would address the safety?

Certainly Steve's study is large, and we

have that data. But what about the other cases, and maybe the FDA would like to comment on that.

DR. MINK: This is the pediatric pneumonia cases that we've identified so far in our review. As I've discussed, it's ongoing.

We have not totaled the cases in this column intentionally. There are varying age groups, varying times of follow-up and varying monitoring. So there is no here number on purpose.

What this is to show you is that we have so far identified 37 cases that were pediatric age group, okay? This is not a two to one randomization of FluMist to placebo. These are just the cases that we've identified so far in FluMist and the cases that we've identified so far in placebo.

For denominators, we have that for AV006. This is a study that we mentioned before was enrollment began in August and continued through November. These kids are 15 to 71 months of age. In that context less than 21 days the relative risk was 1.98 with these confidence intervals of .36 to 24.78.

We have also provided relative risk for study AV019, which is similar to those presented by the sponsor. This is children from 1 to 17 years. This study was performed starting in October and we

have data through December 31st -- or maybe April 30th, I can't remember for sure. But I think it was December 31st in the interim analysis for this.

From 1 to 17 year olds who received FluMist from October through the end of December, the relative risk was .83 with the confidence intervals of .3 and 2.28 showing for pneumonia is less than 21 days. Okay?

We can't give you a percentage here, nor do we mean to imply that there is twice as many in the FluMist group than the placebo groups. These are just the studies in which we've been able to look for cases. And in those studies we found 37 and 12. These don't even have placebo groups, so you can't compare them. Okay?

CHAIRMAN DAUM: So what is your conclusion from that?

DR. MINK: My conclusion in AV006 is there's a signal and we need to understand more. In AV019 there's not a signal and we need to understand more. But, like I emphasized, it's different follow-up, different analysis -- I'm sorry. Different age groups. And Aviron is working with us to finish this analysis.

CHAIRMAN DAUM: Are these data on this

slide regarding pneumonia in the BLA?

DR. MINK: That's what I'm showing you. This is all I have in the BLA. But the data for pneumonia wasn't submitted summarized. We've been doing a search for it. And this doesn't include bronchitis and bronchiolitis, which could be coded very differently. We don't have predefined definitions of pneumonia.

Like in 019 it's ICD09 codes that the caregiver is giving. In AV112 year one it's line listings from some of the parents. In AV06 there's a combination of how the pneumonia is being identified.

This is a lot of differences put together.

CHAIRMAN DAUM: Dr. Katz and Dr. Geber.

MR. KATZ: I think she just answered my question. It doesn't mean a positive chest film. It doesn't mean a positive blood culture. It just means somebody wrote down pneumonia.

DR. MINK: A healthcare provider.

CHAIRMAN DAUM: Dr. Geber, please.

DR. GEBER: No, I think that that's all. I think that for some of these studies that are listed here, we don't have complete study reports yet. And we did receive some case report forms, I believe, from all of these subjects last week. So while the

information will be available and we will be able to identify -- I think the point that we're trying to make is that in our review of study AV006 for year one, when we looked at pneumonia, these are the cases that we found, although they hadn't been summarized.

And then the next point we're trying to make is that there are a lot of outstanding data to us, much that the sponsor has presented, some which have been submitted but have been submitted in subsequent submissions after October and are not completely reviewed by us.

So, I think our review is incomplete and we can't draw yet any conclusions one way or the other about pneumonia at this point. And we recognize that the sponsor will work with us to provide additional data, but we don't have those data just yet.

CHAIRMAN DAUM: Thank you, Dr. Geber.

Dr. Greenberg, you wanted to make a comment about pneumonia.

DR. GREENBERG: I totally agree that we will continue to work with the FDA to define these issues with great clarity.

I would only take slight issue with saying that they detected a signal when there is no statistical association really of a signal. And I

think we need to look carefully at all the data and what you have seen is a very large trial from Kaiser, controlled, randomized, double blind placebo control. And I just want to remind you, although you've heard it several times, that there's no increase in pneumonia and there's no clustering temporally of pneumonia. And I won't show you the data, but from the cases AV012 in those two years there is also no time clustering of those cases vis-à-vis the receipt of FluMist.

The FDA will evaluate that as they need to independently, but I think that will give them confidence that there isn't a signal there as well.

CHAIRMAN DAUM: Thank you very much. I'd like to return to the Committee at this point and see whether here are other safety issues that we want clarified or discussed in some more depth, or data from our FDA or sponsored colleagues.

Dr. Stephens?

DR. STEPHENS: My question concerns the allantoic fluid "placebo" or diluent. And I don't think we've discussed that enough, at least in my view.

Is there any data from the manufacturer on just the "placebo" or the allantoic fluid in

comparison was saline or a different placebo? Because I guess my one concern I have is the reactogenicity of that material and we're constantly referring to it as a placebo when in essence in may not be.

DR. GREENBERG: Let me give you one piece of data which may or may not satisfy your curiosity. So when these questions were raised last night, what we did is look at upper respiratory tract infection in the Kaiser study in the placebos. Why don't we go to that one first.

And reasoned that if there was reactogenicity in the upper respiratory tract you would see it early after the receipt placebo and it would fall off. And this is the URI coding by day in the Kaiser study across the 42 day window. And at least by my analysis, there is no -- it does not look like there is increased reactogenicity temporally associated with giving placebo. Now, this isn't controlled, this is just looking at placebo over time; that's the control.

DR. MINK: These are kids that seek medical attention or have an SAE?

DR. GREENBERG: Yes. No, these are people who in anyway, as Dr. Black mentioned, have an MAE or coded in the Kaiser study for the diagnoses of URI.

CHAIRMAN DAUM: I think you're both saying the same thing.

Dr. Myers and then Dr. Snider.

DR. MYERS: On the same issue in the adult study runny nose is reported in 26 percent of the allantoic control group. Have you done a similar analysis?

DR. GREENBERG: Yes, we have, Dr. Myers.

You've never been a straight man for me before so -- and will never be again.

So if you look here, this just the 7 day reactogenicity period. The placebo runny nose really doesn't change over time. And, again, my conclusion from this data is that this is not reactogenicity. I would expect reactogenicity due to an irritant, a nonreplicating irritant of some form or another to be higher temporally clustered with the time of administration. And so I respectfully differ with the FDA as to whether there is evidence of reactogenicity with the allantoic fluid.

CHAIRMAN DAUM: Thank you, Dr. Greenberg.

Dr. Snider, and Ms. Fisher, then Dr. Cox.

DR. SNIDER: On that same point, Harry, then I have trouble understanding page 10 of Mr. Mendelman's presentation on safety in children in

which it shows percent with runny nose, nasal congestion day zero running around a little above 10 percent. Then both groups having an increase in the next few days and then coming back down.

DR. GOLDBERG: Bob Belshe I think did a great job. I am not a pediatrician, I'm an internist, but I am a parent and I do remember -- well, I'm not going to use the aphorism for these kids. But I do remember when my kids were little. But, Bob, say it again because you say it better than I do.

DR. BELSHE: Okay. These children, and this is the dataset that includes AV006 and -- all integrated data. The AV006 dataset looked exactly like this that's reported in the New England Journal.

On day zero children are enrolled who do not have runny noses at time zero. Now, ten percent of the mothers check runny nose later that day on the case report form. And on day 1 and day 2 and so forth it's around 20 percent and it stays fairly level at 20 percent of the duration of the study.

So what we're seeing here is a return to the mean of children, a typical child about 20 percent will have a runny nose on any given day. That's what we're showing.

CHAIRMAN DAUM: Thank you, Dr. Belshe.

DR. SNIDER: Just to further clarify. Then what you're saying is that the other ten percent were screened out the first day?

DR. BELSHE: That's right. If they had significant runny nose -- if they had runny nose detected by the study nurse, they weren't vaccinated.

CHAIRMAN DAUM: Thank you very much.

Ms. Fisher?

MS. FISHER: Yes. Encephalitis and encephalopathy are known rare, although rare reactions after vaccination. And certainly Guillain Barrè Syndrome has been associated with at least swine flu vaccine.

I was wondering if you think that the numbers are not large enough to detect the occurrence of encephalitis and encephalopathy, Guillain-Barrè Syndrome, polynephephritis after this vaccine? And if you don't think the numbers are large enough, how large they would have to be to perhaps detect that?

DR. GREENBERG: I don't have the size calculation on the top of my head, and I'm surrounded by epidemiologists, so I'm anxious about this.

Taking Guillain-Barrè as one of the examples, I would imagine you're going to need immense databases to rule out an association of Guillain-

Barrè. I mean, literally the country because the rate of Guillain-Barrè with influenza is small enough. So it's something like that. It's really huge.

Dr. Mendelman whose better at this than me, says about one in a million.

CHAIRMAN DAUM: Thank you.

Dr. Cox?

DR. COX: Yes. I wanted to bring up an issue that's related to the transmissibility of the vaccine virus, and it has to do with the inadvertent exposure of immunocompromised individuals, and in particular severely immunocompromised individuals to the vaccine.

And I just would like to make a comment to say that influenza can, indeed, be very serious disease in bone marrow transplant recipients and others who are severely immunocompromised. There are fairly high rates of mortality and hospitalization and serious disease. So this is something that we would need to be concerned about.

And so I'm just wondering if there is any way to address this to screen people who are receiving the vaccine very carefully, and so on, or if there are any studies that might bare on this particular concern?

CHAIRMAN DAUM: Hear from the sponsor and/or FDA on that question.

DR. GREENBERG: Dr. Mendelman presented to you the two small studies in HIV patients, patients infected with the HIV virus. And as you're aware, we do not have any studies of safety of FluMist in severely immunocompromised people such as somebody who has just had a bone marrow transplant. I think that's a factual answer.

Obviously, prevention of wild-type influenza is of great benefit and prevention of wild-type influenza in the family of people having bone marrow transplantation would of great benefit.

And in the one case of transmission that we had, I would remind you that the virus had the phenotype of the original vaccine and was associated with no change in the child and was associated with no illness different than the other people in that study.

CHAIRMAN DAUM: Thank you.

Dr. Schild, please.

DR. SCHILD: Mr. Chairman, I'd like to share with you some thoughts on genetics in relationship to safety and transmissibility.

I mean the given information is that the cold-adapted phenotype is conveyed by four of the

genes PA, PB 1 and 2 and M.

We've quite a lot of interesting information about the identification of the lesions in those genes related to the phenotype. However, that information is based on sort of consensus sequence data. And there are now new methods of very rapid analysis of viral populations. Polio virus is a very good paradigm for that. There are now routine methods developed greatly in this particular study for analyzing populations of live attenuated polio vaccine which can pick up a very small proportion of the particles which show nucleotide changes that might make them likely to revert to virulence.

So the question is how much have population genetics been applied to these vaccines? The sort of question one would like to answer is for any vaccine bulk population, how many of the particles contain all four attenuated lesions. I think that can be answered.

And also, we can use those techniques to look at the genetics of viruses excreted from those individuals who have longer term excretion and perhaps have febrile responses and in relation to transmissibility.

And I also think there is a need for more

attention to be paid --- more studies from looking for potential for transmissibility to susceptible individuals.

CHAIRMAN DAUM: So the question, as I understand is, at least as a bacteriologist we would ask the question do all members of the bacterial population contain the same phenotype with respect to these mutations? There must be an equivalent to that in virusland.

Can someone address that question from the sponsors?

DR. GREENBERG: Dr. Zamb, if you're not going to address it, I'm not.

What Dr. Zamb said to you I think is the most important thing from the -- outside of polio, one of the most extensive studies of mutations in RNA viruses shed by humans that my colleagues at Wyeth have carried out, and that is in none of the shed viruses were there mutations in any of the sites associated with attenuation of the shed viruses. And, of course, that's interesting and good.

DR. ZAMB: That is in fact true.

DR. GREENBERG: Do you have any more data to add to what -- I think that's the best data we have.

DR. ZAMB: And it's very comprehensive.

I believe you were attempting to suggest that we develop Naprocam analysis for the individual mutations. I think the ideal circumstance is to better characterize, in fact, in specific nucleotides and their actions and call that adaption temperature sensitivity and attenuation. And I think the best way of doing that is by plasma-based rescue where you can alter individual nucleotides and then construct viruses with those individual changes and in specific combinations to evaluate the individual mutations that are thought to be associated with that, and confirm that theory. And I think that's the most efficient way of doing that, and we're beginning to pursue this at this moment.

DR. GREENBERG: Both Wyeth and Aviron are pursuing that.

CHAIRMAN DAUM: One follow-up question. Go ahead.

DR. SCHILD: The first part of the comment was really how genetically homogeneous is your virus--your master virus received or your vaccines pools in relationship to the attenuated lesions in individual infectious units?

DR. ZAMB: Again, what we need first to do

is to clearly identify those specific nucleotides that do confer the attenuated phenotype. And then once those are identified we can in fact do clonal analysis on those populations to determine the frequency of nucleotide differences, if there are any at those positions.

CHAIRMAN DAUM: Thank you very much.

I'd like to press the Committee at this point once more for other issues to clarify before we vote on question 2 regarding safety? I think we're almost there, but there be one or two more issues out there.

Dr. Myers?

DR. MYERS: To go back to the normal allantoic fluid placebo. Have similar analysis as we just saw been done for GI events including abdominal pain?

DR. GREENBERG: Dr. Myers, could you ask that question again because I'm not sure I understood it?

DR. MYERS: The number of GI events, including abdominal pain, seem to me to be more frequent than I would expect in both the FluMist and in the placebo groups. And so I was wondering if you'd done the same type of analysis for that?

DR. GREENBERG: I think we're trying to call that up right now. Isn't this what they want?

DR. BLACK: This is what we have. This is what I showed you already. We have looked at abdominal pain in the final analysis dataset, and that is still -- still is significantly elevated, as it was before. And the time frame of the cases is still spread out. We didn't make a graph, because we didn't think we really adding any new information because basically the numerators and denominators change, but the rates are still within the same range.

Does that answer your question?

CHAIRMAN DAUM: Thank you very much.

Dr. Griffin?

DR. GRIFFIN: I just want to ask one clarifying question, and I just can't find the chart at the moment. And that's if you look at the deaths occurred overall in any of these studies, the majority of them are all in the COPD study group. But in my recollection of that data, you had similar numbers of deaths in those that got FluMist as those that got the placebo.

What I couldn't remember is over what period of time and whether there's thought to be any link to just getting this kind of vaccine and COPD.

It just seemed like a lot of people died.

DR. MENDELMAN: The trial was conducted by the VA Cooperative Studies Group. And as they submitted it and completed the protocol, they were going to collect all AEs for the entire duration of the trial, including serious adverse events.

As the trial moved forward, they continued to collect all the serious adverse events so they continued to report death throughout the trial period.

It started in October of 1998 and went through until May -- the spring season.

So looking at the temporal relationship of death, there -- well, to reconcile the one number with the FDA's document, but there were 3 deaths within 28 days of receipt of inactivated vaccine and FluMist and there were five in the placebo group within 28 days that also got inactivated vaccine within 28 days.

The FDA document has four versus four. And the VA Cooperative Studies program study is still undergoing analysis. But those are the numbers that they provided to us.

So we believe the temporal relationship is what should be looked at. Some of individuals, obviously, died very far out after there'd be any plausibility.

CHAIRMAN DAUM: Thank you, Dr. Mendelman.

DR. GRIFFIN: So the majority of people died within -- so it's about a six month follow-up?

DR. MENDELMAN: Yes.

DR. GRIFFIN: And so I guess I would -- what it looks like is that you have about five or six people dying every month along the whole period of time in both groups, is that what you're telling me?

DR. MENDELMAN: Sixty-four deaths over that period of time.

DR. GREENBERG: Diane, this population had a mean age of 68 and head real COPD, and these were people with significant health issues.

DR. GRIFFIN: But they weren't hospitalized at the time. They were entered, they were outpatients and then developed these problems over the next six months?

DR. GREENBERG: Yes.

CHAIRMAN DAUM: Thank you very much.

We're moving toward dealing with the question. I would like to actually start dealing with the question unless there are additional unaddressed issues.

Thank you, George, et.al. It's up on the screen again. I don't think we need a refresher as to

its language, we've heard it a couple of times.

Dr. Steinhoff, are you up there? I can't see you. Would you be willing to start the Committee deliberation with regard to your view of this question?

DR. STEINHOFF: Yes, I guess I could start.

We've seen and discussed just now a lot of data and the question is are the data adequate to support the safety in the population for which an indication is being sought.

Overall, my feeling is that we have a lot of data on safety. I have to say that there are still some questions that don't appear to me to have been fully analyzed, and we understand that both groups, the FDA and the sponsor, are working together to provide full information and then undertake an analysis.

We've heard different results from different studies which were undertaken with different methodologies, so it's a little hard to compare a finding in one study that didn't show up in another study.

The safety data that is of sort of major concern, which is the lower respiratory illness or

asthma, it's either incomplete in terms of the pneumonia or with the asthma it's in very small age group and doesn't appear elsewhere, at least in the California data.

So I guess my feeling is that I'd be willing to say yes to this question with a qualification that the analyses that have been mentioned mostly around the issue of pneumonia, and as the others speak they can remember the other ones, those should be completed.

CHAIRMAN DAUM: Thank you very kindly.

DR. GRIFFIN: Bob, can I clarify just one thing.

DR. STEINHOFF: But, of course.

DR. GRIFFIN: So the indication that's being sought for 1 to 64 years of age, that at all qualified by healthy individuals 1 to 64 years of age or is that all individuals 1 to 64 years of age?

CHAIRMAN DAUM: Dr. Geber, please.

DR. GEBER: So the indication reads -- I mean, we will work with the sponsor, obviously, but we'd appreciate your comments. The indication is 1 to 64 years of age. There is a contraindication section which specifies that it counter indicated in subjects with immunosuppression and specifically listed are

those who might immunosuppressed due to therapeutic interventions, and then more broadly those that might be expected to have a lower antibody level to the FluMist vaccine. But specific categories for which, for instance the flu, the influenza vaccine is recommend, you know, that have been mentioned by the Committee as renal dialysis, diabetics, they're not specifically mentioned. They could be inferred to be included in that contraindication section. Any thoughts that you might have on that would be --

CHAIRMAN DAUM: Dr. Greenberg, you want to discuss the indication, that's all?

DR. GREENBERG: I think we'll work with the FDA, but we are seeking an indication for healthy children. As I said in my introduction and in all of our slides, healthy children and adults 1 to 64 years of age.

CHAIRMAN DAUM: Thank you. Dr. Midthun wants to comment on this, and then we'll return to you, Dr. Steinhoff. I do see you.

DR. MIDTHUN: Could we clarify how the indication relates to individuals with asthma? Can you hear me? Could you clarify how your indication relates to individuals with asthma and how you would be seeking viewing those right for your current

indications sought?

DR. MENDELMAN: Again, we will obviously work with the FDA, but we believe that the data we have in children and adults with asthma is not sufficient to give FluMist to adults or children with a diagnoses of asthma.

CHAIRMAN DAUM: Thank you.

Dr. Steinhoff, you wanted to comment on this issue, please.

DR. STEINHOFF: The question really is in vote 1 we were talking about a very specific age group, and this question also is confined to a highly specific age group. And I don't know if you want a qualification on that.

CHAIRMAN DAUM: One to sixty-four years.

DR. STEINHOFF: Yes.

CHAIRMAN DAUM: I suppose you're right, but if you want to qualify your answer, you're perfectly welcome to. Everything you say is being recorded and, believe me, played and replayed by many folks with interest in this room.

So, you're welcome to make comments or qualify your answer totally at your pleasure.

DR. STEINHOFF: Well, I guess the comment I want to make is that there clearly is a substantial

difference of opinion regarding the efficacy data, especially in that youngest age group. And the safety data may be less crucial in terms of that age group, but obviously if efficacy is not good in a certain age group and safety is, it has different kinds of implications.

My own feeling is that the safety data we've seen does appear to be fairly supportive on --

CHAIRMAN DAUM: You said so.

DR. STEINHOFF: Yes.

CHAIRMAN DAUM: Yes. Just to review, there are actually -- maybe we should spend a minute here because I thought everyone had it straight. But let's just go over it for a minute.

There's three parts to this question which everyone ought to be reflective about. One is the actual question: Are the data adequate to support the safety of FluMist between 1 and 64 years of age? Yes/no. Comments, of course.

Then, secondly, please discuss the adequacy of the data in two groups: Less than 2 and greater or equal to 50.

And then the third part applies only if you vote no, I guess, for the first part. If the data are not adequate for specific age ranges, please

discuss would additional data should be requested.

So all comments are welcome, of course, but these issues need to be addressed, and I think that's been done.

Dr. Edwards?

DR. EDWARDS: I want to be comfortable that the children and adults who are recommended because of high risk conditions to receive inactivated vaccine each year still are recommended to receive inactivated vaccine. And I think that's what you're saying, that the indication will be for those in individuals who are not recommending? Okay.

I think that it's hard to give a vaccine to a child. If you aren't comfortable with the efficacy, it's hard to recommend that they be given in that age range. So I think consistent with my previous statements, I feel most comfortable with 15 months to 64 years.

I do have questions about the pneumonia, and I think that that has to be very, very carefully looked at. Each case has to be dissected and perhaps even reviewed by an expert in pediatric infectious disease to make sure that everyone is comfortable with that, particularly that it relates to the youngest children. And I think additional safety data

regarding the pneumonia question in the group less than two years is very important.

I think there is cause for concern in the asthma data. I don't think it's certainly clear yet that there is a major risk, but I think this is a group who should be immunized and I think that if the vaccine is to be given, that practitioners should very clearly state that if the children have asthma, that this is not the vaccine they should be getting. They should be getting the inactivated vaccine. Although I must parenthetically add that only 30 percent of children with asthma, even in the best situations, get the inactivated vaccine.

I think that the data for individuals who are over 50 if they are healthy, and I think for those of us over 50 a number of us think we remain healthy, but if they are in a age group that they would be recommended to receive the inactivated vaccine, they should receive the vaccine that is indicated for them. So I think in that group and barring COPD, which I don't think you're asking for, that with the caveats that the FDA needs to review, particularly the pneumonia data and fully assess the asthma data, I think the data is adequate.

CHAIRMAN DAUM: Thank you.

Dr. Myers?

DR. MYERS: I think at this time the data is not adequate to support the safety of FluMist. That said, I think it is likely to prove to be safe, but the data and the data analysis are incomplete. And until those analysis for lower respiratory infection, for asthma and some of the other studies have been completed, which when they're completed my answer will be different. But in the absence of the completion of those analysis, I don't think the data is complete.

I don't think the data, for example, is adequate to conclude the safety for children previously diagnosed with asthma. I think we need increased data for children under 24 months of age.

I am concerned the data, the recommendation for adults over the age of 50 because we don't have data on those who have underlying medical conditions. Not necessarily that they be immunosuppressed, but those with diabetes, renal disease and so on.

So, I guess again I'd like to emphasize, I really think that when these analyses are done, it is likely that I would vote differently.

I think that we must have the definition

of the flock for endogenous retroviruses, in addition.

And then just as a comment, I find it difficult to conclude not significant from a placebo comparison for entities such as conjunctivitis and so on when the comparison is to normal allantoic fluid. Although I think the areas where irritation from normal allantoic fluid may occur may be minor adverse events, and therefore it may not be an issue. I just would say as a caution that that's the placebo.

CHAIRMAN DAUM: Thank you very much, Marty.

Ted?

DR. EICKHOFF: I'm still a little uncertain as to the correct interpretation of the indications. Should I read for use in healthy children and health adults? Thank you.

CHAIRMAN DAUM: That's what we're hearing from the sponsor, so I think that people should factor that in, although comments about underlying diseased adults and children are welcome. But the question is about healthy children and adults ages 1 through 64.

DR. EICKHOFF: I'm reassured by the safety considerations regarding this product. And my vote is going to be yes, but if the Chair will permit me to do it, it's going to be a provisional yes because there

are issues that are yet to be resolved with regard to pneumonia and with regard to asthma.

I look, as we all did, the Kaiser Permanente data in 019 and it looks reassuring, and it appears to be the most cohesive dataset that we deal with. So I'm greatly reassured, at least as far as pneumonia is concerned by that dataset.

The FDA analysis suggests some other problems, and we are cautioned that this is an ongoing analysis. And so my provisional yes is given with the anticipation that these issues between FDA and the sponsor will be satisfactorily resolved.

The same issue applies to asthma, perhaps even more so. But, again, I'm reassured by the data provided in the Kaiser Permanente study which, again, I think is the most cohesive dataset. But that issue, too, needs resolution between FDA and the sponsor. When those are done, my vote will change from provisional yes to yes, assuming satisfactory resolution of those issues.

There is the lingering uncertainty that I have about turning this attenuated vaccine loose on the general population wondering what's going to combine with what. And I'm sure Dr. Schild will have some more to say on that issue, so I'll defer to him.

Thank you.

CHAIRMAN DAUM: Thank you.

Dr. Cox.

DR. COX: I think that the overall safety profile of FluMist is very good, but I have some lingering concerns about what we've seen relative to asthma, pneumonia. And I think that we all know that the data, the analysis are incomplete and we really look forward to seeing a more complete accounting of whether these may be associated with the FluMist.

I think that there's no doubt in my mind that there's some real world issues that have to do with safety that need to be dealt with, and one has come up a number of times in our discussions, and we know that we don't have any data on concurrent administration. And I think that's just an absolutely crucial issue for consideration of safety.

In addition, I continue to be concerned about inadvertent exposure of immunocompromised individuals because we know that the HIV infected individuals who were in the various trials were relatively healthy. And we have no idea how long this virus could replicate in individuals who are severely immunocompromised; if there might be a greater risk for transmission, reversion and reassortment and so

on.

I think that what I would like to say is that in my view the question of concurrent administration of other vaccines is a very, very crucial one and so at this moment I would have to say no. But it's -- again, I'd like to emphasize that I feel the overall safety profile is very good, but there are these lingering questions I think that can be resolved, but I have to vote right now.

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

Dr. Schild, I'm going to ask you to wait one moment, because we're starting to get into airplane time here. So I'm going to ask Dr. Katz to speak next, and then we'll return to you if that's all right.

MR. KATZ: Thank you, Geoffrey. My vote is yes, but that I feel that, one, we need to continue the FDA analyses that we've heard about that are currently in progress of pneumonia and asthma.

Then, secondly, that it's imperative that post-licensure phase four studies be required in order to capture any further data on rare events inapparent in the numbers that are immunized to date. And I'm thinking especially of central nervous system events

which may occur with such rarity. But given what we have now, I would vote yes.

And I've left my proxy with Dr. Griffin for the discussion points.

CHAIRMAN DAUM: Thank you very much, Dr. Katz. We wish you a safe trip home.

And we'll ask Dr. Schild to now speak to us.

DR. SCHILD: Thank you, Chairman.

I think safety can be considered in relationship to the vaccinee as well as the vaccinee's contacts and certainly in relationship to the general population. I think we're asked to vote only in relationship to the licensee on this occasion, but I would like to make some comments about the broader aspects of safety, particular public health safety which I may be straying into question 4, but nevertheless I'll mention this.

On the question of safety in the vaccinee, I think I would give a conditional qualified yes rather along the lines of Dr. Eickhoff; that certainly very careful analysis should be done by FDA of data that is available now and will become available.

The particular issues that I think do need more attention are the asthma issue and the pneumonia

issue.

And also I'm expressing sympathy with Dr. Eickhoff's view. Safety in high risk individual, high risk elderly individuals who I know are not part of the indication, but nevertheless it is something that really needs to be considered. And I really also I must express some sympathy, although I didn't mention it at the time, with the view that maybe inactivated vaccine might be the best way of treating those now, the very high risk elderly individuals.

I do believe that we need more genetic analysis in general, not only of the vaccines, but of the shed virus. And I think we ought to have in the long term much more information on the propensity of the vaccine strains to transmit. We've only heard, I think, of one study on that.

Safety in the general population we're not asked to vote on. It's a very difficult field, so many unknowns. And I think what we can offer is to mount very careful surveillance in the population for any evidence that the vaccine virus may be mutating to virulence, may be continuing to circulate, and so on. That is not mentioned here in the question, but I do think it's one of the things that could be considered. And I know in this country there is a very good system

of strain surveillance and identification both by antigenic means by genetic means.

CHAIRMAN DAUM: Thank you very kindly.

We move on to Dr. Griffin, please.

DR. GRIFFIN: Well, I'm reassured in general about the safety profile of this vaccine, however I do think that we don't have -- I won't say that the data are inadequate, because they may eventually be adequate, but we do not have access to adequate data yet to completely make me feel confident about the safety profile particular in the under 2 year age group. Again, with concomitant immunization, questions of pneumonia, asthma; I just think there are quite a few unresolved issues that may become resolved in even the next few months, although the concomitant immunizations study is just under way. So that may take somewhat more time.

I have a lingering, perhaps irrational concern about what is a very attractive route of immunization, intranasal immunization that comes from my background as a neurovirologist.

Do we have any other vaccines, licensed vaccines that are given by the route? Yes, I mean we just don't have experience. And as I say, it intrinsically is a terrific way to immunize, I just

would want to pay attention to any neurologic complications that could be associated with it. So far it appears there are no indications that that's a particular problem.

So, I think that just based on the fact that I think that the data are as yet -- that we have in hand are inadequate, not because I think that the vaccine itself is not going to prove to be safe, I have to vote no on this question.

CHAIRMAN DAUM: Dr. Griffin, we thank you.

Dr. Stephens?

DR. STEPHENS: I share Diane's vote as a provisional no. I think I, like Dr. Cox and Dr. Myers and Diane feel positive that ultimately this vaccine will be shown to be safe, I just think that there is not enough data at this point to convince me that the answer to the question is yes. Certainly under in the younger age groups, certainly the issue of concomitant vaccines, certainly the issue of those over 50 are areas of concern.

CHAIRMAN DAUM: Thank you, David.

Ms. Fisher?

MS. FISHER: I do not think we should license a new live virus flu vaccine that will be given to children as young as one year old without

adequate pre-licensure safety data in those children.

I'm troubled by the lack of adequate safety data for this vaccine on children under 5 years old, particularly under 2 years old. There's an incomplete understanding of the implications of viral shedding on transmissibility to close contacts, which is particularly important for children who are often in close contact with each other.

For children and adults there are outstanding questions about why there is more influenza-like illness including fever after vaccination as well as whether or not there is a real increased risk of pneumonia, bronchitis and asthma in healthy individuals after vaccine and an even greater risk for these outcomes in acutely or chronically ill individuals.

I believe a practical issue that needs to be resolved is whether variations in the way the vaccine is administered nasally has a significant impact on whether these attenuated viruses can end up being swelled or find their way to the respiratory tract and cause respiratory abdominal or neurological complications.

Certainly given the fact that this vaccine will be administered to children who are already

receiving 3 dozen doses of other vaccines in the first 5 years of life, there can be no confidence in the true safety profile of the vaccine in the real world unless data is generated that includes administration to several thousand children under 5 with genetic diversity over at least 4 years where you measure for all morbidity and mortality outcomes, including evaluation of immunological and genetic integrity and general health and wellness after repeated vaccination.

We have very limited experience using inactivate flu vaccine in children under 5, and it is extremely important to be sure that widespread introduction of an new live virus flu vaccination into this child population will not ultimately negatively impact on their long term general health and wellness, even though it may indeed prevent them from getting the flu short term.

This is a huge step because we are going to be shifting the entire flu vaccination strategy from targeting adults to targeting children, and we had better be sure we're doing this safety.

CHAIRMAN DAUM: Dr. Goldberg, please.

DR. GOLDBERG: Well, from the data presented it appears that this vaccine is safe to the

extent that it's been given. I would vote no at this time. I think all of the issues have been raised, and then I think also we're proposing administering this attenuated live vaccine annually. And I think the data with repeat vaccination is totally inadequate to address long term safety.

Furthermore, the safety that you follow-up in the children studies for 42 days, that post-vaccination, and then in the adult studies for 28 days; that's fine for short term sequelae, but not monitoring for long term sequelae. And with repeat administration you don't know what the cumulative effects will be as well.

I do think this vaccine will turn out to be safe, but from the data we've seen here I think we need more information.

Thank you.

CHAIRMAN DAUM: Steve?

DR. KOHL: I basically concur with the majority of my colleagues. I think and hope that eventually this will turn out to be a safe vaccination, but at this point in time because of what I think we've all discussed in absence of confident data regarding pneumonia, asthma, concomitant immunizations and also for immediate licensure, and

also in terms of post-licensure studies, I would like to see a fairly large study on rare events and also inadvertent immunization of pregnant women.

So for the first number of reasons, I'll have to vote no on this.

CHAIRMAN DAUM: Dr. Snider?

DR. SNIDER: I'm voting provisional, as others did, and I don't know if it's provisional no or provisional yes.

CHAIRMAN DAUM: You know you won't get away with that, Dixie. But let's hear your comments first.

DR. SNIDER: Well, I mean, there are still some outstanding questions. I mean, FDA has indicated that review is ongoing for some of the data, particularly with regard to respiratory events. And a number of people around the table have mentioned concerns around pneumonia, bronchitis, bronchiolitis, asthma.

I think we've been reassured by the sponsor about a number of these issues, but that reassurance is mostly -- has to do with at what level these things are likely to occur. In other words, they're not occurring so frequently that they're showing up in the size trials we've seen, at least

it's not clear that they are, although further analysis may bear out that they are showing up here in sufficient numbers to be statistically significant. But at the moment whether there's a signal or not a signal, there is some data that creates some concern. And I think that concerns derives, in large part, because a lot of biological plausibility I won't go into, but which I'm sure everybody around the table understands.

There's also the issue of the reactogenicity of the placebo and some disagreement between the sponsor and FDA about that issue. I don't think it's a huge issue, but it seems to me that it's important to try to clarify the difference between how much nasal congestion might be caused by the vaccine versus not having anything put in your nose. And it just is a matter of trying to quantitate for parents accurate information so that it's more of an aggravation of not having really good data on that point.

I think it's fairly clear that there is some reactogenicity from the vaccine and we would expect local reactogenicity in the nose from something we put in the nose, just as we get in the arm or in the deltoid or in the thigh; wherever we put vaccines,