FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

VACCINES AND RELATED BIOLOGICAL PRODUCTS
ADVISORY COMMITTEE

OPEN SESSION

Friday,
July 27, 2001

The Committee met at 8:30 a.m. in the Grand Ballroom at the Gaithersburg Holiday Inn, Two Montgomery Village Avenue, Gaithersburg, Maryland, Dr. Robert S. Daum, Chairman presiding.

PRESENT:

ROBERT S. DAUM, MD	Chair
NANCY COX, Ph.D.	Temporary Voting Member
KATHRYN EDWARDS, MD	
THEODORE EICKHOFF, MD	
WALTER L. FAGGETT, MD	
BARBARA LOE FISHER, MD	
SAMUEL L. KATZ, MD	
STEVE KOHL, MD	
JUDITH D. GOLDBERG, Sc.D.	
DIANE E. GRIFFIN, MD	
MARTIN MYERS, MD	Temporary Voting Member
GEOFFREY SCHILD, MD	Temporary Voting Member
MARK STEINHOFF, MD	Temporary Voting Member
DAVID S. STEPHENS, MD	
NANCY CHERRY	Executive Secretary

A-G-E-N-D-A

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

8:39 a.m.

CHAIRMAN DAUM: Good morning. I apologize for banging on a gavel, particularly at this time of the day, but my bell is broken. So, until we have that repaired --

DR. EDWARDS: Maybe that wasn't accidental, Bob.

MS. CHERRY: Someone needs to go to the Mall Of America and get a new one.

CHAIRMAN DAUM: So, we have administrative matters. Let me turn the floor over to Nancy.

MS. CHERRY: I have none.

CHAIRMAN DAUM: We have no administration matters, which is a good thing.

So we'll move right away to asking Dr. Levandowski, whom I've seen, to begin with posing the questions for the Committee's discussion. And then we will talk about further procedure when he's done.

We've been having a huddle on a procedural matter, and the procedural matter just relates to how to divide up this morning's discussion.

What we're going to do is look at the first question, which is a complicated question relating to efficacy of the FluMist vaccine for which

we heard yesterday.

I've then asked Dr. Mink to initiate the Committee's discussion on this first question by summarizing the viewpoint of FDA, what the FDA thinks is important regarding this efficacy question.

And then we will stop and have Committee discussion on the efficacy, and then we'll repeat the whole procedure for question two, which concerns safety.

MS. CHERRY: And then we have an open public hearing somewhere in there.

CHAIRMAN DAUM: And we'll have an open public hearing, Nancy, I promise, somewhere in there.

So, let's roll with question one and Dr. Mink.

DR. MINK: Question for efficacy and the Committee we're asking for a vote: Are the data adequate to support the efficacy of Flu Mist in:

(a) The pediatric and adolescent population from 1 to 17 years of age? If so, please discuss the appropriate schedule, i.e., one dose vs. two doses. If two doses are recommended, please discuss the age range for this regimen and the recommended timing, i.e., the interval for the doses.

Also please discuss the adult population

18 to 64 years of age.

In your discussion please address the adequacy of the challenge data submitted in support of efficacy against H1N1 influenza strains.

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

George, Dr. Daum has asked me to reshow slide 40 from my presentation yesterday.

CHAIRMAN DAUM: Who is George?

DR. MINK: I'm sorry. Any George.

CHAIRMAN DAUM: Good morning, George.

DR. MINK: We got it all down right.

CHAIRMAN DAUM: George, we get a sense of how you're coming.

DR. MINK: The efficacy conclusion from yesterday's presentation, first efficacy against culture confirmed influenza-like illness was demonstrated one or two doses in healthy children from 15 to 17 months of age in year one and again after revaccination in year two.

At one site, however, contrary to protocol when cultures were obtained in the first 11 days after immunization influenza-like illnesses occurred in children who shed cold-adapted influenza viral

strains.

In adults an effectiveness study was performed. We do not have efficacy data against culture confirmed illness in adults. In this effectiveness study in adults there was no significant decrease in any febrile illness during influenza outbreak periods, which was the primary end point in the study.

Secondary end points including sever febrile illness and febrile upper respiratory infections did have demonstrated efficacy, however the lower bound for SFI was 1.4 percent and for FURI was 5.5 percent in CBER-generated confidence intervals.

Also we have no field efficacy data for H1N1 in either the pediatric efficacy trial or in effectiveness experience in adults.

In a challenge virus study performed in pediatrics it was challenged against vaccine strain H1N1. And the adult wild-type challenge there were only about 30 subjects who were in study participation.

Anything else, Dr. Daum?

CHAIRMAN DAUM: No, I think that's a superb start. And we're going to want to use you, of course, and the sponsor's group as a resource in our

discussions, so we may need you to come back.

But you could probably scoot back to the FDA table if you would. And if we could have the lights.

Could we get the question back on and sort of leave it on, George, when you have a moment. This George.

And so now I'd like to have sort of just general Committee discussion regarding this question, number one. And please feel free in your discussion to ask people to show you stuff that you saw yesterday that you want to see again or hear framed again.

And let's sort of do it generally at first, and then we'll begin to focus on the questions themselves.

So, the floor is open. Dr. Goldberg, Dr. Edwards, Dr. Katz.

DR. GOLDBERG: What data do you have about repeated administrations of the vaccine over more than two years? I mean, I think there was a little bit of data shown, but I just want to make sure that I understand all of the data. So how far have you gone with repeated annual administration of this vaccine in adults and in children?

CHAIRMAN DAUM: It's a question for the

sponsor, I guess.

DR. GOLDBERG: Yes.

CHAIRMAN DAUM: This is George also. Yes. It makes it easy for me. You want to see a slide, just ask for George.

DR. MENDELMAN: These are the data in children for repetitive dosing. The 4,771 for second annual season. 1,999 for a third. And 549 for a fourth consecutive season.

CHAIRMAN DAUM: Yes. That's a good way to proceed. We're going to have questions right about this issue, and I still have the sequence with Dr. Edwards next. So Dr. Katz.

DR. GOLDBERG: One more second.

CHAIRMAN DAUM: Sorry. Dr. Goldberg then Dr. Katz.

DR. GOLDBERG: Is there anything in adults and do you have an efficacy data on the third and fourth administrations?

DR. MENDELMAN: The efficacy data is only for the first and the second year, it was a two year study in the efficacy trial on children.

The effectiveness trial on adults is a single year, single season study.

DR. GOLDBERG: Okay. Thank you.

CHAIRMAN DAUM: Dr. Katz, just about this.

MR. KATZ: Just about that slide, Paul. When you give us numbers such as those, those are just the vaccine recipients, not the controls, is that correct? When you say there are 2700 children 1 to 8 years of age; is that 2700 vaccine recipients or 2700 total in the study?

DR. MENDELMAN: Vaccine recipients.

MR. KATZ: Thank you.

DR. MENDELMAN: Individual unique children.

CHAIRMAN DAUM: Dr. Griffin about this slide and then Dr. Schild about this slide. This is a popular slide.

DR. GRIFFIN: Well, I think it's sort of a crucial slide for some of the questions.

And that's whether you have any data on serology on what boosting actually did and how necessary boosting was, because in general these were the same vaccine that was given over and over, right? Or these are different formulas in the first, second, third, and fourth years?

DR. MENDELMAN: In the pediatric trial the H1N1 strain changed between year one and year two. The year three they did not change. In year four they

did change. So, there were several formulations that were given to the children.

In the revaccination in year three it was a safety study only there was no serology in year three, however we did do serology in the fourth study season. And the children in the H1N1 group had a boost in their antibody responses. Most of the children to age 3 in B were already seropositive from prior years of vaccination.

DR. GRIFFIN: We heard the conclusion, but I don't remember seeing the data with respect to the fact that they tended to respond to only two of the components the first time and you really needed a second dose to get a response to all three. Do you have data that you can share with us on that?

DR. MENDELMAN: Yes, and Dr. Belshe's slides in the -- backup, George.

CHAIRMAN DAUM: Dr. Edwards be patient. Your next when we finish this issue.

DR. MENDELMAN: These are the data from the subset and study 006. After two doses of primary vaccine in the first year, you can see the 96 percent seroconversion and baseline seronegative children for the H3N2 in the B strain and the 61 percent seroconversion for the H1N1 strain.

DR. GRIFFIN: This is after two doses?

DR. MENDELMAN: This is after two doses.

DR. GRIFFIN: Do you have any data for what happens after one dose?

DR. MENDELMAN: Oh, sure.

DR. GRIFFIN: I assume it's worse.

DR. MENDELMAN: I can tell you what's in my brain.

DR. GRIFFIN: Okay.

DR. MENDELMAN: The seronegative children after dose one to H1N1 was 16 percent after one dose.

DR. GRIFFIN: 1.6?

DR. MENDELMAN: Sixteen percent.

DR. GRIFFIN: Oh, 16. Okay.

DR. MENDELMAN: And then boosted to the 61 percent as noted on the slide. The response at H3N2 was over 90 percent after the first dose and the response to the B virus was about 89 percent after the first dose.

CHAIRMAN DAUM: So there's a difference with H1N1, obviously, in terms of the --

DR. GRIFFIN: That's the main problem it sounds like.

CHAIRMAN DAUM: This issue. Okay. This issue. Okay.

DR. STEPHENS: In terms of the dose, the one or two doses, the question has to do with efficacy. Because as I recall the efficacy after one dose despite the immunological data was almost equal, is that correct, at least to the H3N2, but --

DR. MENDELMAN: For both the H3N2 and the B, and the one dose cohort the efficacy was at 90 percent for those two strains after a single dose, 88.9 percent.

CHAIRMAN DAUM: But then H1N1 becomes the issue again?

Dr. Kohl?

DR. KOHL: It's reiterating this the same question, and I don't think you can answer it. The question is do you need two immunizations.

DR. MENDELMAN: I'm sorry. State again.

DR. KOHL: The question is do you need two doses for children.

CHAIRMAN DAUM: A rhetorical question.

DR. KOHL: And the data, at least in my mind, is not added by the serological response since you've already shown us that the serological response doesn't necessarily correlate with protection. And it looks like unless you have data that you haven't shown us yet, that there's no efficacy with H1N1 other than

challenge because there weren't any H1N1 in those years.

Per chance, did you challenge any individuals who only got one dose in that pediatric challenge study, or were they all double dosed?

DR. MENDELMAN: Well, they were all revaccinated in the second season.

DR. KOHL: So they were triple dosed?

DR. MENDELMAN: And then the challenge was five to eight months after that second season dose.

DR. KOHL: Okay. The question is do you need more than one immunization to protect against H1N1? And the answer is we don't know?

DR. MENDELMAN: My answer would be to get optimal protection against all three strains, you would need two doses.

DR. KOHL: But you're just saying that; you can't support that?

DR. MENDELMAN: We know that if you have a high immune response for serum HAI, that does correlate with the efficacy. And there are data, as you saw in the adult trial, that in spite of a lack of a response to the H1N1, those adults were still protected against H1N1. In the young seronegative child we want an optimal response to all three strains

and the data we're presenting is that one dose was sufficient for the H3N2 and the B. H1N1 didn't circulate for five years between '95 and this year.

So, it's in a sense a combination vaccine that we want. Going from 16 percent seroconverion to 61 percent would mean to me as a clinician that we're maximizing the response of H1N1 circulated.

DR. GREENBERG: I think Bob Belshe has historical data in his head and has other comments to make about two doses versus one dose.

DR. BELSHE: Yes. For Dr. Kohl, actually I think this data shows that the second dose of at least trivalent vaccine serological shows infection with H1N1 virus after one dose. So this is, in a sense, an equivalent challenge although it's a challenge with trivalent vaccine.

And, George, could you put up the H1N1 historical efficacy data?

Now, there's really quite a good literature on efficacy of H1N1 vaccine. The largest study was actually conducted by Dr. Edwards, and she might want to comment on that as well.

A summary of the 11 efficacy trials with H1N1 vaccine is shown here. The first five are monovalent vaccine and you can see the efficacy has

ranged from 34 percent to 100 percent depending on the study.

Second series of studies are for trials using bivalent H1N1 with H3N2 vaccine, the largest one being Dr. Edwards' study, which showed in year one 78 percent efficacy against H1N1 and in year four of that study in which H1N1 circulated, 91 percent efficacy. That study includes both children and adults.

And then we've presented here the two studies with trivalent vaccine. The children's challenge model, which shows 83 percent efficacy and the adult challenge model, which included H1N1.

CHAIRMAN DAUM: Thank you, Dr. Belshe.

DR. GREENBERG: Bob, do you want to just briefly comment on your historical trials of one dose versus two doses, which was another question?

DR. BELSHE: Yes. We've had an opportunity to examine both bivalent vaccines and trivalent vaccines for one dose versus two doses. And really the best data is from AV006 demonstrating 16 percent serologic response rate with dose one, 61 percent after two doses.

CHAIRMAN DAUM: Thank you.

There are some people here that may have comments about this very issue. I have Drs. Schild,

Myers and Faggett. Are they all about this issue?

DR. SCHILD: Yes, but mine is a more general issue.

CHAIRMAN DAUM: Can you hold then? I'll put you on the general list.

Dr. Myers, this issue?

DR. MYERS: The data is all pooled, and I was wondering if it's possible to see both efficacy and the immunogenicity data specifically for the 12 to 24 month old child?

DR. MENDELMAN: In the FDA briefing document and the slide that Dr. Mink showed yesterday, the efficacy and my memory is 84 percent of the children under two years of age.

CHAIRMAN DAUM: Do you want to see it again, Marty? We can get to work on that while we hear someone else's comment.

CHAIRMAN DAUM: Drs. Mink and Geber, and et al.

DR. MYERS: Well, for example, this is pooling all of the data. We're being asked specifically about a one year recommendation. And the immunogenicity data we just saw was pooled data from 15 months to 71 months. And I suspect the H1N1 response is different in the first year of life than

it is in the third year of life.

CHAIRMAN DAUM: Dr. Mink is mobilizing George and we shall have the data you wish in a moment.

I want to stay fixed on this issue. Dr. Faggett?

DR. FAGGETT: Dr. Myers asked my question already. Thank you.

CHAIRMAN DAUM: Dr. Stephens this issue.

DR. STEPHENS: I have a question concerning the timing of the dose. In the 06 study the timing of the dose was 60 days, yet the proposal is for 30 days? Can you clarify that difference?

DR. MENDELMAN: The timing was 60 plus or minus 16 days. So 46 to 74 days.

DR. STEPHENS: But your request is for 30 days.

DR. MENDELMAN: Correct.

George, can you go to the GMT responses and AV007.

In the lot consistency trial, AV007 we did a sub-analysis. In that study 500 children were dosed. 100 received placebo, the other four groups were three consistency lots 100 children each and a 100 children getting efficacy vaccine. And in that

study children could receive vaccine as early as day 28.

And these are the time interval data. If children got a dose -- where -- day 28 to 41 on this column here compared to if they got day 42 to 60. And you can see the seroconversion rate are similar in this analysis for each of the three strains.

CHAIRMAN DAUM: Thank you. WE're ready to see the data that Dr. Myers asked for. Could we put them up, George, please?

DR. MENDELMAN: If I could just comment. Also in the FDA briefing document they note this analysis in their document.

CHAIRMAN DAUM: Thank you, Dr. Mendelman.

DR. MYERS: And is there any data for 12 through 15 months in the serology.

CHAIRMAN DAUM: Let's look at the data you asked for here first, since they're ready.

DR. MINK: This is the efficacy by age that was requested. I didn't bring a pointer. But to go through, you can see -- thank you.

Under 24 months there were 223 subjects that were in the analysis. Any strain, which includes H3N2 and B -- remember there's no H1N1 field data -- the efficacy against any strain was 84.7 percent. And

what I noted yesterday for you is there are wide confidence intervals, especially against type B. And the reason being that there's such a small number is what we presume.

There's efficacy that was comparable for all of these age groups, but again all the n's are small so some of the confidence intervals, especially against type B, are pretty wide.

Did you want to see gender and ethnicity, too? I don't remember. Slide 15 please.

CHAIRMAN DAUM: Dr. Faggett would like to see that.

DR. MINK: Okay.

CHAIRMAN DAUM: So as long as you're up there, let's do it.

DR. MINK: There were no differences noted in efficacy against any strain for males and females, and they were comparable, obviously, to the analysis for the whole study cohort. Remember this is subjects enrolled in two doses, which is different than the primary n point, which was subjects who had definitely received doses.

And then for ethnicity, there was about 85 percent of the subjects that were caucasian and 155 that were non-caucasian. And the efficacy wasn't

appreciably different between the groups in any strain.

Wide confidence intervals again when the numbers are small.

CHAIRMAN DAUM: Thank you very much.

DR. KOHL: Can I thank you for finally the ethnicity data. We've been asking for that for years and I think is the first time we've ever seen ethnicity data presented to us.

CHAIRMAN DAUM: We're asking both FDA folks and sponsor folks to be very nimble with their data this morning, and I recognize that. We're asking them to put up slides out of sequence and on virtually no notice. And the Committee thanks you in advance, because it's very helpful to our deliberations.

We're going to move on to a different subject now. Dr. Edwards is the next speaker, then Dr. Katz and Dr. Schild.

DR. EDWARDS: Well, I guess the first question that I raised my hand for was how many patients or how many children between 12 months to 15 months have been immunized? This is indicated for 12 months, and I'm not sure I know how many kids 12 to 15 months have been enrolled. So, that was the first question.

And then I did want to comment on the data that Dr. Belshe put up about the study that I conducted and reported in 1994 regarding H1N1.

Maybe I could comment while they're getting the number of children between 12 to months.

I think one of the issues that's really important for people to understand is that the cold-adapted vaccine sometimes will have a much more brisk immune response with the H3N2 and sometimes much more brisk response with the H1N1. And interestingly, our study that we did that was NIH funded that enrolled 5,200 plus people, we found during that time that the H1N1 was very immunogenic and, indeed, generated a much higher -- well, a significantly higher immune response with the cold-adapted vaccine than the H3N2 did, which is really in contrast to what we're seeing in the Aviron study.

So, I think that there is some variability between the strains bearing different H1N1.

Our study was done with the single dose of cold-adapted vaccine in all children. And, in fact, our children only received a one to ten dilatation of the vaccine. So, obviously, a less concentrated vaccine.

In that situation, as Dr. Belshe showed,

we had one year that was matched very nicely with the vaccine strain and one year that was a drift strain. And just as he had mentioned, the efficacy in adults and children was exactly as he sad, 78 and 90 percent for culture confirmed disease.

In contrast, the H3N2, which was less immunogenic that year, in terms of culture confirmed disease, and granted there are many caveats. This is a drop vaccine. We did not have the funding to do the intensive surveillance that was done, so those caveats are all there. But the efficacy with one dose of H3N2 was 59 percent for a drifted strain and 56 percent for a well-matched strain.

So I think that the vaccine does have efficacy after a single dose for H1N1 and for H3N2, even if it's not an optimal immune response. But whether that's what is wanted, whether the optimal response after two dose versus one dose is something we need to discuss more fully.

DR. KOHL: Kathy, is this the same vaccine as Aviron's?

DR. EDWARDS: No, it's not. This is a vaccine made by a different manufacturer; the same master strain, however. And, again, I'm not trying to say this is comparable, but I'm just saying that there

are some differences in the immune response to different vaccines.

CHAIRMAN DAUM: Thank you.

Dr. Katz?

DR. MINK: I can answer the age question if Aviron doesn't have the data. Do you want me to do that one first?

Under 12 to 15 months of age, according to Dr. Rida and our statistical review, we have accountable 200 children in studies in the FDA database.

DR. MENDELMAN: This slide is the updated numbers. The cut off data in the FDA briefing document was as of April 30th.

The statisticians from Aviron are working on the number between 12 and 15. And Dr. Mink, I believe, will be correct; it'll be in that range.

The cut off shown here, 12 to 18 months of age, is 813 FluMist recipients, 19 to 35 months of age 3,395 and then you see the other breakdowns.

CHAIRMAN DAUM: Dr. Mink, do you want to comment?

DR. MINK: I can just give you the numbers that we have in our database, if you'd like.

From 12 to 15 months for FluMist

recipients our n is 200. From 16 to 19 months the n is 507. For 20 to 23 months it's 547. And that gives us a total of 1254 subjects under 24 months of age.

CHAIRMAN DAUM: Not incompatible with these data, just a different way of breaking then down?

DR. MINK: Different age group and an early dataset.

CHAIRMAN DAUM: Thank you.

Now I think we're ready to go on to Dr. Katz.

MR. KATZ: My comment, really, rather than question is a much more generic one. But we've been asked to look at data supporting the efficacy of FluMist. And I'm very comfortable with what we've seen. But I think it has to be made very clear to the public that, you know, influenza is but one infection of what we're going to be coping with. And the overall reduction of acute febrile respiratory illness is going to have to include respiratory sirsal virus, the parainfluenza viruses, the adenoviruses. And my concern is not with the vaccine, but with how it's presented to the public and the health providing community in that there will be great disappointment if we still see lots of febrile respiratory illness,

which we certainly are going to, but it's not going to be due to influenza viruses.

I think it's terribly important to prevent influenza virus illness. And as Paul Glezen and others have shown very convincingly it doesn't even have to be respiratory illness. It can be ill-defined febrile illness, particularly in the younger infants whom we're discussing now.

So, I think there has to be a great deal of clarity whatever the decisions are and however it's eventually presented that we're preventing specifically influenza virus illness and not respiratory disease in daycare centers and in infants in the first years of life.

CHAIRMAN DAUM: We do, of course, have the same problem with the current immunization vaccine schedule, do we not?

MR. KATZ: Right, but it's poorly if at all used in the pediatric age population, except perhaps for high risk children. Whereas, I think the ease of administration of a nasal vaccine and avoiding the pin cushion effect I think will have very definite assets.

And there are already people in the pediatric infectious disease community who are

pushing for universal immunization of infants and children, both to protect them and to interrupt transmission to adults.

CHAIRMAN DAUM: On this point, before I call on Dr. Schild whose next and Dr. Kohl, would someone care to comment about the data in adults that there was no decrease in acute febrile illnesses? I believe those data was taken from a time when influenza virus was very heavily circulating in the community. And vis-à-vis Dr. Katz' question, I was curious as to what comment sponsors or FDA or Committee members, or anyone had about that issue.

DR. GREENBERG: I think Kristin Nichol will comment.

DR. NICHOL: Sure. I would certainly be interested in commenting.

It is absolutely true that the primary n point for the clinical effectiveness trial in health adults did not show a statistically significant reduction as we discussed yesterday. The primary n point or outcome definition that we selected for that trial was any febrile illness. And that was very sensitive but nonspecific outcome.

Recall that this was a clinical effectiveness trial designed to very broadly access

impact across a number of different outcomes, not only illnesses per se, but also health care use.

I think it's important to recognize that even if the primary n point is negative, is there something else that these data can tell us that is important and useful regarding the question does the vaccine work? That is, is the vaccine efficacious, which is a slightly different question from the primary question in the clinical trial, which was is the vaccine clinically effective across a broad range of health economic parameters.

If one is interested in asking does the trial provide useful information on whether or not the vaccine works, is it efficacious, which I believe is the question in front of this Committee, then I think it's important to ask which is the most appropriate outcome definition to look at and by what way it's measured.

And I believe that then one looks at the most specific illness definition that we included as the prespecified definition, and that would be febrile upper respiratory illness. We recognized that when we were looking at different illness definitions in the study planning stage and from some studies published since that trial was conducted, including that Dr.

Arnold Manto published in the Archives of Internal Medicine, I believe last year looking at the positive predictive value of various clinical syndromes; we do believe that the febrile upper respiratory illness definition, which most closely approximates the CDC's ILI surveillance definition, is the most specific for influenza.

So, that's why I look at the most specific illness definition in asking the question does the vaccine work in adult populations rather than it is clinical effective across a number of outcome parameters.

Then the question is what is the most efficient way to measure that. And I'm, perhaps, a bit chagrined in admitting in retrospect we chose for the primary n point only, to look at proportions of people having any event. And recall we were looking at any febrile illness.

Well, it turns out that people can have more than one event because many of the febrile illnesses are not due to influenza. And so if one wants to look at the most efficient way to measure the outcome, one should look at events rates.

So I would propose if the question is does the vaccine work, that one might look at events rate

and in particular at the febrile upper respiratory illness category or the severe febrile categories as being more specific. And if you look at the slide shown here -- I don't have a pointer -- but you can see that the reductions are as they are shown.

I don['t want to shine this in anybody's eyes. With more precise estimates than we saw when we were looking at proportions. And, in fact, the lower confidence bounds for those reductions I have here. I don't have them on the slide. I apologize for that. But for febrile upper respiratory illness, the lower confidence bound for the percent reduction is 12.7 and it goes to 33.2 as the upper bound for the 95 percent confidence interval.

CHAIRMAN DAUM: Thank you very much for that helpful comment. Comment on this point? Dr. Goldberg?

DR. GOLDBERG: Excuse me. Dr. Nichol --

CHAIRMAN DAUM: Dr. Nichol?

DR. GOLDBERG: Am I correct in your saying that for any febrile --

CHAIRMAN DAUM: Dr. Goldberg, if you could get that mike right up close.

DR. GOLDBERG: For any febrile illness you used the proportion of patients with the event? For

essentially first event?

DR. NICHOL: For the primary --

DR. GOLDBERG: And for the others you used an event rate? Is that what --

DR. NICHOL: For the primary outcome a single outcome in measure --

DR. GOLDBERG: Right.

DR. NICHOL: -- we looked at the proportion of people having any febrile event. We also measured the proportion of people having these outcomes as well.

DR. GOLDBERG: Okay.

DR. NICHOL: And we showed that on a previous slide.

The point I'm making is there's a single primary outcome, but then if we're asking --

DR. GOLDBERG: Back up. On this slide am I seeing the effectiveness --

DR. NICHOL: These are event rates. These are event rates.

DR. GOLDBERG: Also for any febrile illness, is that an event rate as well?

DR. NICHOL: These are all event rates.

DR. GOLDBERG: Okay.

DR. NICHOL: The numbers of episodes.

DR. GOLDBERG: That's all.

DR. NICHOL: I'm sorry.

DR. GOLDBERG: Thank you.

CHAIRMAN DAUM: We'd like to move on now. Thank you, Dr. Nichol.

To Dr. Schild, whose been patient and eager to raise a point for our consideration.

DR. SCHILD: A general point, Chairman.

Like Professor Katz, I've found quite a lot of satisfaction in the efficacy data presented yesterday. However, it would be good to see field data for H1N1 virus.

But I'd like to address the issue of the protective efficacy in the face of antigenic and genetic variation of the viruses. We had good data about a two year period of antigenic drift for the H3N2 virus, which showed good cross protection. And I think it would be highly desirable in the long run to know much more about protective efficacy of all three types of vaccine in relationship to progressive antigenic and genetic drift of the virus.

And also in the long run, to be able to relate that sort of information by immunological markers. There's considerable scope for learning much more about the sort of protective efficacy induced by

this virus in terms of antibodies local in circulation and in terms of other markers.

In terms of antigenic variation, I think it would be interesting also to know a bit more about the neuraminidase contribution. These are long term issues. I don't think they're issues that can be resolved within a short period of time.

CHAIRMAN DAUM: There are influenza experts here who might like to say something about that, or we'll just take it as a reflection?

Dr. Schild, we thank you for your reflection.

Dr. Kohl, then Dr. Snider, and Dr. Stephens.

DR. KOHL: We're going to spend a lot of time on side effects later on, I guess. But my question is related to the interaction of side effects and effectiveness. And what I'd specifically like to ask Aviron is do you have any data, since there are a lot of side effects; some of them bothersome. I think there's an increased fever, especially in young children, which might bring these kids into the emergency rooms. There's clearly a huge increase in "a runny nose," which on some occasions might bring very young children in to see their private doc. And

that is balanced by the effectiveness, the number of cases of influenza that are prevented and saving money.

So, have you or any of your colleagues done a time benefit analysis, a cost benefit analysis to see what this is going to do in the trenches to the pediatrician and the pediatric patient?

DR. GREENBERG: Before we answer that question, getting back to how many children between 12 and 15, we were digging through to give you that number. That's 271. I can't remember asked, but you all wanted to know the number.

Steve, the question you asked is about fever and runny nose. And I think the best thing to do would be to call up the -- Paul, you're doing that?

DR. MENDELMAN: Dr. Kohl, I can tell you the number of differences. The percent with low grade fever between vaccine and placebo.

DR. KOHL: No, but that's not what I want. I want to know a cost benefit analysis if it's been done.

DR. MENDELMAN: Well, I understand the question.

DR. KOHL: You had done that for adults and it's included in the packet and $30 looks like a

break even point. What does it look like for kids?

DR. MENDELMAN: Are we talking about economic issues?

DR. KOHL: I'm talking about economic issues.

DR. MENDELMAN: Okay.

DR. KOHL: But it's more than economic issues. It's life issues for pediatricians and pediatric patients.

DR. MENDELMAN: Okay. There's an article coming out in Pediatrics next month. The article is a cost economic analysis based on data from the efficacy trial AV006 and a list of assumptions therein.

The analysis team was Brian Luce's group at Medtap International and the various investigators, Dr. Belshe included and Dr. Zangwill and others who are the investigators in the 06 trial.

There were two numbers. As I remember them, if the parent has to take off time from work for two hours to take the child in for an immunization, the data look identical to data that Dr. Mary Nettleman has published previously with the inactivated vaccine in children. And that is, about $4 to $5 cost savings.

If there's an alternative to give vaccine, like a vaccination clinic where the parent doesn't have to take time from work, again identical to the inactivated vaccine data that Dr. Nettleman and her group has published, it's about $28 cost savings.

CHAIRMAN DAUM: Steve, you could feel free to return to this issue when we get to discussion point four, which is what additional data you would like to see generated. But I'd like to move on to --

DR. GLEZEN: Dr. Daum, could I make a comment that directly responds to Steve's question?

CHAIRMAN DAUM: I think you may.

DR. GLEZEN: I'm Paul Glezen from Texas.

The last slide that Paul showed yesterday looked at the relative risk of visits for acute respiratory disease in zero to 14 days after vaccination and compared it to prevaccine rates and rates 15 days and greater. And now in three years data with almost 15,000 doses administered, the relative risk for a visit for a acute respiratory illness is less than one for all acute respiratory disease categories.

So, from that standpoint we don't see any increased burden on the medical care system by these side reactions to the vaccine.

CHAIRMAN DAUM: Thank you, Dr. Glezen.

Before you sit down, are you today, Dr. Glezen, distinguished academician from Baylor or are you speaking now on the sponsor's behalf?

DR. GLEZEN: Well, I don't know how to separate that.

CHAIRMAN DAUM: Well, we need to know that you can't. So, thank you very much.

Do you have affiliations with the sponsor? We need to know how to interrupt your comments.

DR. GLEZEN: Okay. The study that we're doing in Texas is based on an NIAID grant, but Aviron provides the vaccine and, of course, holds the IND on the vaccine. And we have, obviously, participated in a lot of safety evaluations for Aviron, which will be submitted to the FDA for this consideration.

CHAIRMAN DAUM: I thank you, sir. And thank you for your comments.

Dr. Snider, you wished to make a comment?

DR. SNIDER: I wanted to ask a couple of questions as they relate to efficacy. I know that the manufacturer's not asking for an indication at this time in persons 65 years of age and older. However, there was some data presented or someone alluded to the fact that there was some information available

that suggested that combination of the inactivated vaccine, which we know in the older age groups is not as efficacious as it is in younger age groups, typically that protection might be boosted by having FluMist and the inactivated given in combination. And so although I understand the reason why people over 65 were randomized to placebo in FluMist, I just wondered if there was any data for those over 65 as it relates to receiving both vaccines?

And also had a question about that I haven't raised, and that is -- I mean, I think I know the answer, but I'd like to hear the answer about the concomitant use of antivirals neuraminidase inhibitors, for example?

CHAIRMAN DAUM: Do you want to comment on that?

DR. GREENBERG: There were two questions asked. One was the question about over 65 combination therapy and the other was the susceptibility of these vaccines to antivirals?

DR. SNIDER: Yes.

DR. GREENBERG: So the first question, the combination experiments were mentioned by Dr. Murphy yesterday. And those were not Aviron studies, those were studies carried out by Dr. John Treanor and

colleagues, whose in the audience, And I think Dr. Murphy pretty well summarized them yesterday showing added effect of a combination. But those are not Aviron studies.

If you have a more detailed question, I think you have the PI for those studies here.

As far as the second question goes, we do have antiviral data which I think is being called up. And the vaccine are susceptible both in neuraminidase inhibitors and to the older antivirals rimantadine and amantadine.

DR. SNIDER: Could someone remind me of the magnitude of the marginal benefit of adding FluMist to inactivated?

DR. GREENBERG: Dr. Treanor, can you just step up?

CHAIRMAN DAUM: Before you start, I apologize, we need your name and affiliation.

DR. TREANOR: Okay. John Treanor, University of Rochester in Rochester, New York.

CHAIRMAN DAUM: And relationship with the sponsor?

DR. TREANOR: We have participated in a number of NIH funded studies that involved cold-adapted vaccine in the years prior to it becoming

FluMist, and then also where the vaccine was supplied by Aviron.

And the study that we're referring to here was done quite a number of years ago using a cold-adapted vaccine which was monovalent H3N2, because our observation had been that in nursing homes pretty exclusively in terms of influenza A viruses, we would see outbreaks of H3N2. And so that study randomized nursing home residents to receive inactivated vaccine and then either intranasal placebo or intranasal cold-adapted H3N2 virus. And this was done over a three year period of time.

And in nursing homes where there were outbreaks of influenza A we saw about a 50 percent reduction in the rate of laboratory confirmed respiratory illness due to influenza A in recipients of combined vaccine.

Now, I think, you know, there are obviously several things to keep in mind about that study. It's relatively small. It was designed really as a pilot study and not a pivotal trial and it involved monovalent vaccine in a fairly unique population of nursing home residents who are extraordinarily susceptible to illness due to influenza A in that sort of intense exposure

environment.

CHAIRMAN DAUM: Thank you very much.

Let's move on to Dr. Stephens next. It his about this very issue? Okay. Then I'll put you on the list. There's Dr. Stephens, Dr. Griffin, Dr. Edwards.

DR. SNIDER: Bob, I didn't get an answer to my question.

DR. GREENBERG: I'm sorry.

CHAIRMAN DAUM: Could you speak into the microphone?

DR. GREENBERG: Yes, I put up this slide and the antiviral part? As I said, and maybe it went by too quickly, the vaccines are -- I think I -- we have the two neuraminidase inhibitors here, rimatadine and amantadine. And what you have here are pairs, the wild type parent and the cold-adapted and inhibitions. And as you can see, when the wild type virus has a sensitive neuraminidase A sort and has a sensitive neuraminidase. And the type As are susceptible to amantadine and rimantadine.

And a B virus, do we have that here? Yes. B virus is resistance, as you would expect.

CHAIRMAN DAUM: Thank you.

Maybe I should check. Dr. Snider, does

that take care of your questions? Good.

Dr. Stephens is next and then Dr. Griffin, Dr. Edwards.

DR. STEPHENS: My questions concern efficacy in the older adult population and specifically data in the 50 to 64 year old group. I think that's the other end of the spectrum that there may be limited data concerning efficacy.

And the second question concerns efficacy in immuno-compromised populations, which is an area we haven't heard a lot of data on at this point.

CHAIRMAN DAUM: Let's hear the answer to that and remember that it isn't really part of question one, but might be something to revisit under discussion point number four.

DR. STEPHENS: It is part of the question. It's part B.

CHAIRMAN DAUM: Let's hear the answer to that, because it's an important part of question one.

DR. GREENBERG: We're not totally seamless in calling up slides.

DR. NICHOL: Forgive me if I'm creating a little delay here in moving forward and asking some questions.

With regard to the clinical effectiveness

trial in the healthy working adults, a subgroup analysis has been done using both an under 40 and greater or equal to 40 age split, which approximates a 50/50 split in terms of the age distribution, the participants.

We've also looked at an over 50 versus under 50 split, and there's no evidence of a decrement in the benefit of the vaccination in the older age group, as I recall, in any of the outcomes that were looked at. Because of the subgroup analysis some of the numbers, obviously, are small. But in terms of interaction between age and effectiveness, there's no evidence of an interaction.

Does that --

DR. STEPHENS: Do you have this broken down between 50 and 64 is the specific question?

DR. NICHOL: Yes. I'm sorry, I guess that's where I created some confusion. This is the 40 split and then these are -- it's not quite the way I was expecting the data to come up, but this is an analysis looking at the 50 over versus under 50 showing statistically significant p-values for effectiveness. But what the question really is, I believe, is is there a difference in effectiveness between under 50 and 50 and over. And there's no

evidence of fall-off in effectiveness. Those p-values when comparing under 50 to 50 and over are generally all about .5 or greater.

Does that --

DR. STEPHENS: Yes, that's helpful. And the n number on these data?

DR. GREENBERG: The numbers over 50 were what, Paul? The numbers are getting smaller.

DR. MENDELMAN: The numbers are approximately 439 FluMist recipients and 200 plus placebo recipients in that analysis that you just saw, 50 to 64.

And this is the analysis you just asked for, and Kristin, if you could present that?

DR. NICHOL: Right. What we've shown here in terms of percent reduction and outcomes, the comparisons are between under 50 versus 50 and over. So it's a question of is there a difference in effectiveness. And you could look at occurrence of illness or days of illness across all of the various outcome definitions. You'll see that the -- oh, I'm sorry. The n's are up there.

The n's are 3,920 for under 50 for all participants and 641 for participants 50 years of age and over. And again, as you'll look across the rows

there, the p-values are for differences in efficacy or effectiveness between the age groups.

CHAIRMAN DAUM: A couple of those comparisons the p-values are significant. Do you want to make any comment on those or not?

DR. NICHOL: The ones that are significant here are in the categories of missed work or healthcare provider visits where it looks as if there was some difference by age group. And I will just note that in those cases, it appears as if the benefit was greater in the older age group both for the category of febrile upper respiratory illness.

CHAIRMAN DAUM: The healthcare provider was --

DR. NICHOL: Pardon me?

DR. DAUM: The healthcare provider is --

DR. NICHOL: Right, both missed worked and healthcare provider visits looked as if there was a greater reduction in the older age group.

CHAIRMAN DAUM: Thank you. That was pretty nimble.

Dr. Griffin?

DR. STEPHENS: A second part of the question --

CHAIRMAN DAUM: Sorry.

DR. STEPHENS: -- had to do with the immuno-compromised --

CHAIRMAN DAUM: These two partners are getting to me a little bit. I'm sorry. You want to state the question again, David.

DR. STEPHENS: Well, my concern, we've heard a little bit of data about the HIV -- there was a small study in the HIV population. There is some VA data. But I mean, obviously, influenza is an important issue in immuno-compromised populations, and I just wanted to feel reassured, if you will, that the efficacy in those populations, renal failure for example, diabetes; those populations in adults that may benefit most from this vaccine. Do you have data?

DR. GREENBERG: No, we don't. We do not have efficacy data in those high risk populations.

CHAIRMAN DAUM: And it's keying in on that part of what you said that I thought you could reraise that as part of discussion point four what additional data are needed. And I agree with you.

DR. GREENBERG: I do want to remind you, although I know you know it, we're not seeking an indication for those populations.

CHAIRMAN DAUM: Dr. Edwards?

DR. EDWARDS: Yes. I wanted to talk a

little bit about a practical issue, and that's because I'm a mother and also a pediatrician.

I know that many times children have runny noses constantly. So the practical issues of the administration of the vaccine in the face of URIs or how is a pediatrician or a family practitioner going to -- what kind of instructions practically do you have? And do you have any data if there is some runny nose present whether the take is okay or whether adverse events are unacceptable? I know we're not talking about safety. I'm just talking about efficacy. But if you have a little safety, you might want to throw it in.

CHAIRMAN DAUM: We wouldn't be offended.

DR. BELSHE: There is no backup slide on this, but there is some anecdotal data.

First of all, let me comment a little bit about the way in which we collected data and the children given a placebo versus vaccine, the normal allantoic fluid.

I got the impression that people were concerned that normal allantoic fluid was causing 20 percent runny nose. That's not the case. We enroll children and selected only children without a runny nose at time zero on day zero, and then gave them

vaccine or allantoic fluid internasally. And by the time those children get home, the mother's check on the diary card on day zero 10 percent of the time that children have runny nose. And then on day two it goes up to 20 percent and it stays at 20 percent for the duration of the diary card.

So what we're seeing is a return to normal baseline rate of 20 percent runny nose in children on any given day. And so it's not the normal allantoic fluid, in my opinion, that's causing that 20 percent rhinorrhea, it's just the nature of children 20 percent of the time have a runny nose.

So, in year four of the efficacy field trial we did enroll a small new cohort and changed the entry criteria so that they could be enrolled and have runny nose. And there is just a handful of data on that, and the data do not suggest, although it is almost anecdotal to be so small, that runny nose in anyway inhibits response to the FluMist. There's no inhibition.

CHAIRMAN DAUM: No inhibition of what?

DR. BELSHE: In a small number.

CHAIRMAN DAUM: Of what? Of immune response or --

DR. BELSHE: Of antibody response to

FluMist.

CHAIRMAN DAUM: Thank you, Dr. Belshe. That was a helpful orientation.

Is there other Committee input on this question one? Dr. Griffin?

DR. GRIFFIN: Part of question 1(a) is if two doses are recommended, please discuss the age range for this regiment and the recommended timing of the doses.

Okay. We talked a little bit about the timing, but I haven't seen any data that supports the current request that it be for children under the age of 9. And so I just wondered where that data comes from that chooses that cut off point for two doses before 9 and once does after?

DR. MENDELMAN: In part, we accepted the epidemiological data and the decisions of the inactivated vaccine for two doses to be administered to children under 9 years of age if they've not been previously vaccinated. And then children over 9 would receive a single dose.

And Dr. Glezen in the audience could comment further. I believe he presented data at ACIP and possibly to this Committee in the past. I think Paul would be the right person to address that

epidemiologically.

CHAIRMAN DAUM: Would you like to hear that, Dr. Griffin?

DR. GRIFFIN: Yes, please.

CHAIRMAN DAUM: Okay. Dr. Glezen, are you available, willing?

DR. GLEZEN: Yes. Paul Glezen.

We've looked at this in relation to the recommendation for inactivated vaccine, and I think that's the origin of this recommendation is that traditionally inactivated vaccine we recommend two doses for kids under 9.

We considered this related to when natural priming occurs. Because if a child has been primed by natural infection with flu, they respond very well to inactivated vaccine now we're talking about, not live. And in our longitudinal studies of children in the Houston Family Study, and I know Bill Gruber had some data and we talked about this at the time. We found that almost all children have had experience with all three circulating strains by the time they enter school at 5 or 6 years of age. And we thought that this could be safely dropped. But for some reason or other when I proposed this, there was some technical reason that had to do with studies of -- well, I can't

remember. But it was rejected. And the rejection came from an objection by the FDA liaison to the ACIP at that time, I remember.

But basically the studies show that kids respond very well. Now, when it comes to the live attenuated vaccine our experience is that a single dose, and when you look at the data for one dose, that mostly comes from Houston. We found that one dose is effective. In all our previous studies we've used a single dose. And whether we're talking H1N1 or B or H3, we've found that one dose has provided very good protection so that we haven't felt the necessity to use two doses for any of the kids. But I'll leave that argument until later.

DR. GREENBERG: Can I just --

CHAIRMAN DAUM: On this very point?

DR. GREENBERG: Yes.

CHAIRMAN DAUM: Okay.

DR. GREENBERG: I just wanted to clarify for Diane and for the Committee, it's two doses for children under the age of 9 for the first time. Once they have received the vaccine, it's one dose.

CHAIRMAN DAUM: Dr. Eickhoff, this very point.

DR. EICKHOFF: A question for Dr. Glezen.

Would you be content with just a single dose for a 15 month old child?

DR. GLEZEN: My main consideration is public health implications. I think that being the current state of affairs that if we gave a 1,000 kids a single dose, we'd be a lot better off in giving 500 kids two doses for the community and our general health status. And it's pretty hard from a public health standpoint to recommend two doses when we're not doing a very good delivering vaccine to our total population. So if we can get single dose to everybody, we'll be a lot better off.

CHAIRMAN DAUM: But that's not the choice before the Committee. We're asking you to --

DR. GLEZEN: Yes, I understand that. I understand that.

CHAIRMAN DAUM: step into a perfect world where there's a 100 percent coverage and everyone does the right thing. Do we need one or two doses?

DR. GLEZEN: Right. Well, I've been tempted to get up several times when you've talked about H1N1, because this past winter we gave vaccine in the face of an H1N1 epidemic in Texas. 5,000 kids were given H1N1 New Caledonia strain. This was a new variant and previous studies had shown very little

cross protection by previous H1N1 strains. And we were quite delighted to find that a single dose resulted in apparent good protection from our unblinded study in that we only saw one breakthrough. And if we looked at the culture positive illness in age eligible kids in the same community and compared it to culture positive illnesses in vaccine recipients, and this is a rough very crude estimate of efficacy, it would have been 91 percent protection against H1N1 culture positive illness in our study last winter.

And that was a total of several hundred kids being cultured, so that I feel very comfortable, the efficacy standing point with one dose in any age group.

DR. KOHL: Paul, these were previously unvaccinated. Paul Glezen. These were previously unvaccinated children who got one dose of vaccine?

DR. MINK: And the youngest age group:

DR. GLEZEN: The youngest, 18 months. And the youngest -- over 2,000 got their first dose. And there were 3,000 -- we had the data broken down by whether or not they got vaccine 98, 99 or 2000, whether they had multiple doses and all that. And the protection looks good for both delivery of vaccine in 99 or 2000.

CHAIRMAN DAUM: Dr. Griffin had a comment or question for Dr. Glezen also? No. A comment on this issue?

DR. GRIFFIN: Yes. I just want to make sure I understand that what the basis of the data on which we're being asked to vote, basically, on a two dose schedule and the age range which a two dose schedule would be recommended. And it's my understanding that this is based purely on the ACIP -- those CDC recommendations for the inactivated vaccine and that there are no specific data addressing this point from Aviron.

CHAIRMAN DAUM: Well, I think we heard some about sero-conversion rates for H1N1 with one and two doses. And I think --

DR. GRIFFIN: No, we didn't that broken down by age and so we didn't have that broken down by age in this range from, you know, under two, under three, under four -- you know.

CHAIRMAN DAUM: Let's take that point to the finish line. Do we have those data broken down by age, because they're obviously very important to this issue?

DR. GREENBERG: We don't have it on a disk, but we can get it. It's in -- we have it, but

we don't have in front of us.

Are you saying we can get it and bring it to the Committee? So can we just table that. Can Diane wait --

CHAIRMAN DAUM: We can. We can.

I have Dr. Katz and Steinhoff scheduled as the next two. I'd like to try and ask the Committee now to really bring their thoughts to bear on question one and to focus now on comments that have to do with your ability to directly deal with this question.

What I'd like to do is have issues that haven't been raised and need clarification flushed out in the next few minutes. Then go to the open public hearing, which you must do before a vote, and then vote on this question one. Because we need to spend time on question two, the safety question, the same depth as this and it's very important that we come to some closure.

So, I have Dr. Katz and Steinhoff scheduled to speak. We hope that Dr. Greenberg, et al, can provide these serology data for us on the two dose one dose issue. And then I'd ask additional speakers to really address question 1, issues that haven't been raised.

Dr. Katz?

MR. KATZ: I'll defer to the Congressman from Maryland.

DR. STEINHOFF: I'm not a congressman, thank you very much.

Actually, this is an observation about the two dose for the first time immunization of infants. It's an observation.

And that is if you want to do that and if you think about the child as the child goes through time, if you ask for two doses and then another dose the next year, which is the intention, that child will get three doses in a 12 month period.

If you say well one dose is enough, and from what I've seen it looks like one dose probably is enough in terms of effectiveness and efficacy, perhaps not for immunogenicity. If one dose is enough, then that child will get two doses within a 12 month period.

CHAIRMAN DAUM: Thank you. That's very helpful.

Are we ready? Okay, give me a signal or something, that's what to do.

As we approach the thinking on the question, I would remind the Committee to try and do a mental gymnastics exercise which is very important.

And that is to consider in your voting on this question and dealing with it the data that are submitted in the BLA. We've heard a lot of data, some in it, some not in it and I'm not I must say 100 percent certain myself which is which. And we might ask Dr. Mink and Geber and anyone else at the table to speak to that issue before we actually come to it. But the Committee is asked to reflect on data on the BLA in addressing these questions.

Dr. Edwards?

DR. EDWARDS: I think one of the problems that I'm having is trying to separate what has been presented for the licensee of this product and the bulk or a lot of data that has existed before with a slightly different product. And also the data that is still out there that we hope will shed some light on some of the struggles we're having.

I think we're being asked to license a vaccine -- or to recommend the licensing of a vaccination for children that are one to two in age and we have 200 children that are in that group.

We're being asked to vote whether one dose is adequate and the data that we have with this product is, at least in 006, is less than 200 children.

So we're being asked to make important decisions on really relatively small numbers. That's not to say that the previous experience wouldn't suggest that one dose may be adequate and that it may be adequate in young children. But I think it's very difficult to know, and perhaps this is just rewording what you were just warning us about, what we are to comment on.

CHAIRMAN DAUM: Thank you very much. I must say before we go to Dr. Greenberg, I know you're there, we are not voting to license anything. And it's very important we understand that.

DR. EDWARDS: I know. I'm sorry. I know what I'm supposed to be doing, so I'm sorry I misspoke.

CHAIRMAN DAUM: But it's important that everybody understand. We are voting merely to advice the FDA of our opinions about the questions that we're being asked. And so it's an important distinction.

Dr. Greenberg?

DR. GREENBERG: I was confused by Dr. Edwards comments. It's 1812 under 2 years of age. I wasn't sure whether you said there was 200 under 2 years of age.

DR. EDWARDS: No.

DR. MINK: For efficacy minus --

DR. GREENBERG: Yes, right exactly correct.

DR. MINK: For efficacy data the --

DR. GREENBERG: And the second thing is the efficacy data, you've seen our efficacy data. There is no more efficacy data coming in.

DR. MENDELMAN: There are four trials, and Dr. Mink showed these yesterday on her slide. In the BLA that was filed at the end of October, that is study AV006, the two year efficacy data. Study 11, which is the H1N1 challenge data. And then the two trials in adults, AV003 that Dr. Nichol presented yesterday and AV009. Those are the data to support licensure as we're proposing it for adults and children.

The data Dr. Glezen noted to you, which is NIH grant, it's a community protection trial in children 18 months to 18 years of age multi-year.

And the data Dr. Glezen was noting to you is the effectiveness data of the cold-adapted vaccine FluMist in the trial that he's conducting. Those data have not been presented to the FDA. And in our discussions with the FDA Dr. Glezen's trial is a large safety trial.

In our discussions with the FDA we were not asking for herd immunity claim based on Dr. Glezen's study when that study was filed several years ago.

So that data is available to the community. The ACIP and eventually it will be published for the readership and for public health issues. It's nice to know the data that Paul's quoting, but it is not needed for the application.

CHAIRMAN DAUM: Dr. Katz, this very issue.

MR. KATZ: Now the lower half of that slide, Paul, I don't understand. It's 9 to 17 years and then it says 12 to 18 months and 19 to 35 months.

DR. GREENBERG: You've found a mistake.

MR. KATZ: I really only wanted the numbers, Harry.

DR. MENDELMAN: Let me have the pointer. Thank you. Okay.

The numbers are over 12,000 children 1 to 8 and over 6,000 children 9 to 17. So this is in error. And over 19,000 children total.

We probably better, George, to go back to the other slide.

This is the table that the FDA has in their briefing document as of April 30th and we wanted

to update it with the current numbers in the database for the Committee. And the numbers as noted to you, 1812 under 2 years of age. And on the next slide, if you just focus on the children under 3 years of age -- George, could you go back to the prior slide? Thank you. It's 813 children 12 to 18 months of age and over 3,000 children 19 to 35 months of age.

Dr. Mink is correct, there's 265, whatever the number I gave Dr. Greenberg, children between 12 and 15 months of age. So 600 children are over 15 months of age in this cohort.

Historically we have looked at the data with the cold-adapted vaccine with the same master donor virus. The numbers are 800 children under 18 months of age and approximately 265 children under 12 months of age. Historical data, not Aviron data, not under review by the FDA the number is 271 in the 12 t 15 month age group.

CHAIRMAN DAUM: Thank you.

Dr. Snider, you had a new comment about question one that we haven't discussed before.

DR. SNIDER: I had a question because with all the data I'm tending to get lost, but this is not a one time vaccine, presumably an annual vaccine we would anticipate based on our experience with

inactivated vaccine that the efficacy may vary from year to year and with different types.

I'm trying to remember how many years of efficacy data we have for the different age groups, if the sponsor could remind me of that, I would be most appreciative.

CHAIRMAN DAUM: Let's ask Dr. Mink first to respond to that?

DR. MINK: I want to restate what Dr. Edwards said, that the number of children from 15 to 24 months in the efficacy trial was around 230 plus or minus. So those kids, that's for efficacy data, those are the total number that submitted in the BLA. And then the next year, they're all a year older.

So I don't have those final figures off the top of my head, but probably Aviron has those.

DR. GEBER: And if I could just add, I think that there is confusion about what data are in the BLA and what are not. It's perhaps, as Dr. Mendelman has said in his first discussion of it, a little bit easier for the efficacy data.

The only studies under consideration and submitted to the FDA that are going to be submitted in the current plans to the FDA are: The AV006 years one and two; the AV011, which was the vaccine challenge

study in children; AV009, which was the effectiveness study, and; AV003, which was the wild-type challenge study in adults.

These other data are not under consideration by us. They've of interest and helpful to you, but not in our decision regarding licensure. And so we would like -- our comment is if you could focus in your discussion in your vote on those data.

CHAIRMAN DAUM: Thank you, Dr. Geber.

Dr. Katz, please?

MR. KATZ: A great deal of the questions in the last moments have really related to the very young children and this, obviously, is focused in part because of the evidence that's been presented of the morbidity of influenza infection in that age group. This may belong in discussion point 4, but the question that occurs to me is we're talking about 12 to 15 months of age, that's when we give MMR. And the question is, are there any studies that have been done with simultaneous administration of vaccine along with another live virus preparation?

CHAIRMAN DAUM: Varicella might also be added into that question.

MR. KATZ: It eventually will be MMRV.

CHAIRMAN DAUM: We still give Varicella

now.

DR. MENDELMAN: There's a study ongoing now, it's study AV018 it's in children 12 to 15 months of age. The projected sample size to address the question is it safe to give MMR Varivax and FluMist together? Is it immunogenetic for both of the standard vaccines, is it also as immunogenetic for FluMist recipients. So that study has approximately 200 children enrolled of the 1200 proposed. And based on enrollment and timing, those data in that age group would not be available for at least another year.

MR. KATZ: Thank you.

CHAIRMAN DAUM: And you're right, of course, it is definitely an additional data issue that should be put on the list.

Dr. Katz? What's your name? Kohl. Sorry.

DR. KOHL: This goes specifically to the question Sam asked. Does Steve Black have any data to this issue and the Kaiser Group, did they have any concomitant immunizations with the live vaccines?

DR. BLACK: No.

CHAIRMAN DAUM: Thank you very much.

DR. MINK: And the youngest age in that study was 18 months also.

CHAIRMAN DAUM: Thank you, Dr. Mink.

DR. MINK: I'm sorry. It was one year to 17 years.

DR. BLACK: The age group went down to one year, but concomitant vaccines were excluded.

DR. MENDELMAN: In all of our trials we by protocol precluded an inactivated vaccine being administered within two weeks and a live viral vaccine being administered within 30 days.

CHAIRMAN DAUM: Thank you.

I'd like to maybe take a break, from the discussion that is, and ask for the open public hearing to go on. And then, hopefully, Dr. Greenberg will have these data that we're seeking ready. And then we can begin to consider the question dead on.

So, let's go to the open public hearing.

As I understand it, we have two scheduled speakers. And we call on the first one, Dr. Bart Classen. Is Dr. Classen here? Good morning.

DR. CLASSEN: My name is Bart Classen. I'm President and CEO of Classen Immunotherapies. We do vaccine safety work.

I was impressed by really the lack --

CHAIRMAN DAUM: Do you have any affiliations with the sponsor? We need to know that.

DR. CLASSEN: No affiliation with the sponsor.

CHAIRMAN DAUM: Thank you.

DR. CLASSEN: I was really sort of impressed by the lack of long term safety in this data that was presented yesterday. And I would like to remind the panel that you cannot determine the safety of a vaccine based on solely on 42 days of follow up. Attenuated viruses have different chronic adverse event profiles in the wild viruses. And there's also concern about contaminated viruses and contaminating DNA in this production process.

It's also important to remember that in the target population there's very, very low mortality or chronic sequelae from influenza. And I would urge the FDA and urge the panel that before their approval of this vaccine, that the infrastructure is in place to look at the long term safety of this product, including the effect on many chronic diseases that we are seeing that have been linked to vaccines and are epidemic in this country now, including asthma, autism and diabetes.

Thank you for the opportunity to speak.

CHAIRMAN DAUM: And, Dr. Classen, as always we're grateful for your comments. Thank you.

Let's move on to the second scheduled speaker, who is Dr. Paul Glezen. Dr. Glezen, could you also remind us who you are and your affiliations with the sponsor?

DR. GLEZEN: Thank you, Mr. Chairman.

I'm Paul Glezen, Professor at Baylor College of Medicine.

The main things I want to address concern our community study in Texas, which is an NIH sponsored grant and the vaccine is provided by Aviron and as such, we've had a lot of interaction with Aviron, the sponsor of this application in preparing safety data and assessments. But I do not have any interest in Aviron financially and I'm not a consultant for Aviron or have any other connection other than our collaborative efforts in this trial.

When I prepared my remarks I did not anticipate the questions that were raised yesterday concerning safety. And I wanted to just clarify the study that we're doing and how we're assessing safety, because this information will be submitted along with the application eventually.

As you all know, this is an open label trial where we are attempting to immunize the children 18 months to 18 years in a community, Temple-Belton,

in Texas. It's a community of about 70,000 people. And there are approximately 20,000 age eligible children in that community, so it's a fairly large undertaking.

The focus of a safety assessment has been on the ascertainment of SAEs in the first 42 days after vaccination. And there are several levels of our ascertainment.

One is we give the parents a laminated card telling them what to report and how to report it. We give them a refrigerator magnet. They've either had a postcard follow-up at 6 weeks to let us know that everything was okay or there is a telephone contact. And the follow-up has been at least 98 percent for that.

Now, in addition most of these subjects are patients of Scott & White Clinic, which is a large multi-specialty clinic located in Temple. And because of this availability, we on a monthly basis enter in the medical record numbers of all of the subjects and search the medical records for any encounter, particularly emergency room or hospital encounters. And so we are searching not just for the 42 days, but 42 days after the last dose of vaccine has been administered for all of the subjects. So we do have

fairly long term surveillance for serious adverse event for the large majority of the children in our study who are patients of Scott & White Clinic.

Now, the secondary assessment has looked at the occurrences of illnesses including LRI that might be associated with natural influenza virus infection. And one of these searches includes what we would consider rare events such as encephalitis, myocarditis, pericarditis, Guillain-Barrè Syndrome, febrile seizures, anaphylaxis and whatever. And in that particular population we have found none of these rare events occurring within 42 days of vaccination for the children who are patients of the Scott & White Clinic.

Now, the analysis for medically attended acute respiratory illness, or just the common acute respiratory illnesses associated with flu, the structure of the study was suggested by Marie Griffin, who is a member of the DSMB appointed by NIAID for our study. And in this analysis we look for all of the common acute respiratory disease diagnoses; upper respiratory illness, lower respiratory illness and otitis media and sinusitis.

What we do is compare the relative risk then for the occurrence of these events, and this is

a medically attended now. We're looking for visits to the clinic. Zero to 14 days after administration of the vaccine and we compare that in the same population to their pre-vaccine experience, and then 15 and over days after vaccination. And this is done for the period beginning with the day that the first dose of vaccine is given until 42 days after the last dose of vaccine is given.

So, for each year this encompasses a period of four to five months.

Now, as shown in the slide that Paul reshowed this morning, for the first two years we found a relative risk less than one for each of the acute respiratory disease categories, including LRI. And we've now had a preliminary look at year three, which shows the same thing. And this then includes a total of almost 15,000 doses administered to 9,700 children over a three year period.

We could probably refine this data if there's specific questions about pneumonia or about different age groups. But we don't have all this now.

And I will say that the date, of course, is controlled by season since we know that during the period we're administering vaccine, the incidents of these different acute respiratory illnesses increases

as we approach mid-winter and also by age, of course. So it's controlled, it's a Poisson regression type analysis controlling for both season and age.

The other question I wanted to clarify is yesterday in the FDA presentation they said that we accepted children with asthma. I want to qualify that. We exclude children who have moderate or severe asthma. We have included children who have mild intermittent reactive airway disease who defined by not on chronic therapy and not having had treatment for asthma in the emergency room or the hospital for the prior year before vaccination.

And in that study, also, of those children with mild intermittent asthma, we haven't seen any increase in any of the respiratory events in the first 14 days after vaccination.

Now, I'd like to just resume to the points that I wanted to emphasize about peripheral matters, or not really peripheral, but more public health matters that relate to the possible licensure of this vaccine.

First, I want to say that I support the application for licensure of the live attenuated vaccine. And there are two considerations which I think make this particularly important at this time.

One is the vaccine supply. At a time when the priorities for annual influenza vaccination have been broadened to include everyone over 50 years of age, we have been stymied by late delivery of vaccine and for influenza, late delivery is essentially no vaccine.

Even before the change and recommendations, we did not produce sufficient vaccine to cover all the persons given priority for vaccination. Suddenly the inactivated vaccine supply appears vulnerable. Persons concerned about global supplies of influenza vaccine have stated that live attenuated vaccine can be produced in quantity more readily than inactivated vaccine.

Availability of a live attenuated vaccine would not change the priorities for use of inactivated vaccine for high risk patients. However, it would allow clinics to reserve inactivated vaccine for high risk patients and at the same time not deny protection for healthy persons who can receive the live attenuated preparation.

I also wanted to emphasize the importance for instituting some sort of protection for children. The FluMist efficacy trials have focused attention on the role of influenza viruses in acute lower

respiratory tract infections of children. To put this information into perspective, I would like to quickly review data on global disease burden recently published by the JAMA by Michaud, et. al., from the Harvard Medical School.

Now, I hope I can press the right button here. Which one is it? Yes, it's a slide. Oh, okay. There it is. All right. I'm sorry, I had the wrong one.

This is an analysis of global disease burden that's based on the top ten causes of disability-adjusted life-years or DALYs. DALYs for disease or health conditions are calculated that the sum of years of life lost due to premature death and due to disability. DALYs incorporate a discount rate for time preference and an age weighing factor that take into account the higher social value given young adults in most societies.

One important implication is that DALYs weigh the burden of disease for children and the items here that particularly relate to children are lower respiratory tract infections, perinatal conditions, diarrheal disease, vaccine-preventable disease and nutritional deficiencies. Less then those of young adults, for example, HIV.

Now, furthermore, since the number of deaths listed for LRI are those that are estimated globally for children less than 5 years of age, that's about 4 million deaths a year in children less than 5 years of age, this ranking completely disregards pneumonia and influenza mortality of predominately the elderly that is used in the U.S. and many other countries to measure the impact of influenza epidemics.

And for pathogens that contribute to LRI mortality, obviously influenza is only one of many, but it is the most important. And, of course, it's the only one for which we have a method for prevention.

Now, I'd like to say, though, that to put this into some sort of context and what we ought to be thinking about, if we had a pandemic next year which had anything like the pathogenicity of the 1918 flu, we'd see a greater number of DALYs than all of the top 10 here combined caused solely by influenza. So that has to be part of our consideration also.

Now, the authors state that there's a strong case for the U.S. to invest in health research to reduce the major causes of burden of diseases that are not treatable or preventable with the current mix of interventions and healthcare delivery systems both

nationally and globally. This has happened with HIV and AIDS. So when you look at the funds invested in AIDS research per DALY, it's $85 per DALY. However, when we look at acute respiratory disease down here, you can see that it's only .50 cents. So we've come, I think, far short of our obligation to carry out research that might ameliorate this problem.

Now although mortality from LRI is low in U.S. children, serious morbidity is extremely high. This graph illustrates surveillance at Texas Children's Hospital in Houston for 1998/1999. And you can see the peak of visits through the emergency room here corresponds and correlates with the occurrence of influenza. This is the surveillance for influenza that's illustration here at the hospital. And this is the hospitalization peak that's associated in children with the influenza epidemic.

Now, this peak of visits here correlates not only at Texas Children's, but nationally with periods when emergency rooms are clogged up, when hospital beds are full and when the hospitals must go on drive-by status, as Texas Children's frequently does.

The hospitalization rates attributable to influenza based on the viral surveillance are as high

in children less than 5, if you include all this, as for elderly adults during flu epidemics. So the rates are very high. And, in fact, the rates in older children equal the rates of adults with chronic underlying conditions under 65 years of age. And only about 20 percent of these children have underlying conditions, so these are mainly healthy children who are hospitalized during influenza epidemics.

This shows the rates for Medicaid children in Tennessee. This was published by Kathy Neuzil last year the New England Journal. And these are extremely high rates for the low income kids. And this is almost as high as the rates that we've seen with RS virus in Medicaid kids. For RS virus it's about 7 percent. For flu it's about 5 percent. And they went to great effort in their study to eliminate periods of time in their analysis when RS virus was circulating. So they tried to limit this analysis just to periods when influenza virus was active.

So it's clear that healthy children are susceptible and vulnerable to serious complications. And they also found appreciable numbers of outpatient visits and courses of antibiotics related to influenza virus infection.

So I think that there's good evidence that

children could benefit from universal immunization.

Now, one obvious deficiency of the current influenza control program is the lack of protection for infants who have the highest complication rate from influenza virus infection. Numerous studies have shown that children develop poor immune responses to both licensed and activated vaccine and the live attenuated vaccines. However, this can be remedied by full implementation of current or proposed controlled measures. Influenza immunization is recommended currently for women who will be in the second or third trimester of pregnancy during the influenza season. Relevant antibodies generated by this immunization are transmitted to the infant and should provide significant protection during the first six months of life. The effectiveness of maternal immunization for infant protection needs to be confirmed. But then the infants would also benefit by a universal immunization by older children such as demonstrated in the recent CDC trial of children in day care showing that there was secondary benefit to household contacts by preventing spread in those kids. So if the older kids are immunized, actively immunized with the live attenuated vaccine, then there should be sufficient indirect protection combining this with maternal

immunization for the infants who are at the highest risk of influenza virus infection.

So, in conclusion I would certainly support the application of the sponsors of this because I think this will facilitate a recommendation for universal immunization of children.

Thank you.

CHAIRMAN DAUM: Thank you very much, Dr. Glezen, for taking the time to come and share your thoughts with us.

It's 10:25 here in the Eastern time zone, and we're going to take a short ten minute break. We will begin 10:35 with the Committee addressing the question.

(Whereupon, the proceedings went off the record at 10:25 a.m. and resumed at 10:35 a.m.)

CHAIRMAN DAUM: Could everybody please get themselves settled so we can get to work?

Before the break one of the questions that was raised had to do with immune response in young children. Some new data or some data have been circulated to us for review. And perhaps Harry or Paul want to quickly walk us through what this sheet shows as Nancy passes it out.

Are these data in the BLA?

DR. MENDELMAN: Yes.

CHAIRMAN DAUM: Yes. Thank you.

DR. GEBER: Yes, they are.

DR. MENDELMAN: Okay. In order to address the question, the statisticians are working fast and furious.

Part of the issue around immunogenicity with the strain changes from year to year is how do you summarize an H1 when it's changed or an H3 or B. So what we've done is go to the data at hand from the study AV007, which was the lot consistency trial. And these are two tables were taken from the clinical study report that was submitted in the license application the end of October. So maybe you could turn to the back table 42 first.

DR. EDWARDS: I don't think we have this table on this side.

DR. MENDELMAN: Okay. We're getting more copies.

DR. EDWARDS: Okay.

MS. CHERRY: There are more copies coming.

DR. MENDELMAN: So let me just try to introduce it. This trial was conducted in children 12 to 36 months at the Southern Kaiser UCLA HMO with Dr. Kent Zangwill and Joe Ward as the PIs.

The age breakdown is 12 to 17 months, 18 to 23 months and 24 to 36 months.

And Dr. Janet Wittes of Statistics Collaborative was involved with this analysis and can also speak to these.

If you look at table 42, the second page of what was handed out to you, it shows the serum HAI titer prior to any vaccination by lot and the efficacy vaccine was one of the arms of the trial and placebo.

And the scatter I think you can see here is that in this trial of this year, whether you're 12 to 17 months, 18 to 23 or 24 to 36 months, most of the children, if not all, had an undetected serum HAI titer.

Now the question here I have from my group is -- okay. So you see the H1, the H3 and the B. Oh, it's up here. Okay. You won't be able to see this.

CHAIRMAN DAUM: Remember that few besides yourself can see that as you point these out.

DR. MENDELMAN: Right. Okay.

The three age groups big ticket 12 to 17, 18 to 23 and 24 to 36 months. And the strain designation, H1N1, H3N2 and B are noted here as H1, H3 and B.

The point is really to look at the titer

less than one to four and you see that these are numbers of children. So, most of the children, just look at the H1, 17 of the 18 children have no detectable titer in this lot before they get dosed. If you look at H1 here, 24 to 24 are seronegative, 19 of 19 are seronegative before receiving this lot. 12 of 12 are seronegative to H1 and the placebo 28 of 28 are seronegative.

Similarly for the H3, and I'll just go through the youngest age group. 14 of 18 are seronegative for the H3 to this lot. 18 of 24 are seronegative. 15 of 19 are seronegative to H3 for lot 3. The efficacy vaccine 10 of 12 are seronegative.

And for the B, likewise the children are seronegative before entering the trial.

If you look at the 18 to 23 month olds, it's still the case; that if you look at the number of participants in the next row down, titer less than one to four, they're all unprotected based on serum HAI.

That's just telling you that based on these three age groups they'll all entering the trial without antibody to the various strains.

Now, if you look at table 64, which is the first page, and this again it's broken by lot and I just think it's easiest to focus on the row that says

rate --

CHAIRMAN DAUM: Excuse me. Before you go on, can you just go back to table 42 for a minute? I'm probably having trouble interpreting it.

DR. MENDELMAN: Okay.

CHAIRMAN DAUM: But it looks to me like the children sort of have a binomial, it's not the right word, by biphasic distribution when they either have no antibody or undetectable antibody, or lots. Is that not the way you see it, particularly the 24 to 36 and 18 to 23 month old kids?

DR. MENDELMAN: Could you repeat that analysis?

CHAIRMAN DAUM: I don't know, it's really not an analysis.

DR. GREENBERG: Bob, I'm just looking at this. Obviously, this has just come up. But, yes, but you are correct, but I think Paul has -- that is absolutely correct. The point I think Paul was getting at is that the large percentage that were seronegative in these groups.

CHAIRMAN DAUM: And that point is clear. But there's a substantial minority have antibody.

Okay. Let's go on, Paul. Thanks.

DR. MENDELMAN: Okay. Understood,

correct.

So the next slide, table 64 presents the immune response to two doses, which is the proposed regiment in the children of this age group. That's now shown up here.

So looking at the 12 to 17 month old children, and I would focus on the rate percent. So 88 percent are sero-converting to lot 1, 100 percent to lot 2, 74 percent to lot 3 for the H1N1.

For the 18 to 23 month old 90 percent sero-converting, 92 percent, 79 percent.

For the 24 to 36 month old 80 percent, 93 percent and 83 percent.

DR. GRIFFIN: Can I just ask for -- oh, that's for H1. Never mind,

DR. MENDELMAN: Okay. For the H3N2 for the 12 to 17 month olds it all 100 percent sero-conversion.

DR. GRIFFIN: But is your definition that of sero-conversion, because these are the same data as before you have a number of children who start out as already seropositive; that you've had a fourfold rise over an above what they had or this is the rate that is seropositive?

DR. MENDELMAN: They all start out

seronegative in this table.

DR. GRIFFIN: Oh. So you're taking only the sero-negative?

DR. MENDELMAN: Yes.

DR. GRIFFIN: So you have 20 or 30 percent that were seropositive.

DR. MENDELMAN: They're not in this table?

DR. GRIFFIN: Okay.

DR. MENDELMAN: They're not presented. It's only those that have no antibody.

So for the H3N2 they're all sero-converting at 12 to 17 months of age. At 18 to 23 nearly all are sero-converting, 196, 100 percent. And the 24 to 36 months likewise.

In the B virus -- and can you move this up, George? The 12 to 17 months all a 100 percent sero-conversion of those three lots. 93 percent in the 18 to 23 month olds, 100 and a 100 and all 100 percent to the 24 to 36 month olds.

So we see that there's also the efficacy vaccine and the placebo you can see for comparison. But the immune response overall looks similar to two doses of the live attenuated vaccine at each of these three cuts in the age group.

CHAIRMAN DAUM: One clarifying question,

please. If in the case of someone with no antibody to start with, or below the limit of detection and sero-conversion is a fourfold increase, how do you do the math there?

DR. MENDELMAN: It's less than one to four -- or one to four is detectable. If it's less than one to four, that's given a 2. And then if it gets to--

CHAIRMAN DAUM: Thank you.

DR. GREENBERG: I don't want to slow this Committee down anymore. I'm almost forgetting why we did this, but I think it was to show response rate in our youngest, whether response rate to vaccine in the youngest people was similar to older children.

DR. GRIFFIN: If it was in answer to my question, I was trying to figure out what percentage of children needed two doses at the different ages versus one dose.

DR. STEINHOFF: But this is all two doses.

DR. BELSHE: Could we return to that question just a minute, Harry, just to put a perspective on the data you've seen?

CHAIRMAN DAUM: Bob, what are you going to speak to here?

DR. BELSHE: Diane's question was what's

the benefit of two doses versus one dose by age.

CHAIRMAN DAUM: Okay. Please.

DR. BELSHE: And the way I would address that is to say what we need to know is the percentage of children who are seronegative to both H3N2 and H1N1 virus. Because it's the second dose in those initially doubly seronegative that's important to add that additional antibody response to H1N1.

And so it was really the first table that Dr. Mendelman showed, table 42, that's relevant. And what this shows is that in the -- as children get older in the H3N2 era they're requiring antibody to H3N2. And in a different era, it's going to be different.

But that in the three age ranges showed up to 36 months of age, there's a fairly high proportion, about 50 percent of children by the oldest group shown, were still seronegative to H3N2 and nearly all of them were seronegative to H1N1. So about 50 percent of children up through those age ranges would benefit from two doses.

CHAIRMAN DAUM: And there isn't similar data with post-dose one, I presume?

DR. BELSHE: There is similar data for post-dose one in the efficacy field trial.

CHAIRMAN DAUM: But not from this table?

DR. BELSHE: And we actually discussed this briefly in the New England Journal of Medicine article. But the actual data aren't shown, so you'll have to rely on my memory. And that was children under 2 years of age in the efficacy field trial, only 20 percent had antibody to H3N2 and virtually 100 percent, it was 97 or something like that percent, were seronegative to H1N1.

By age five 80 percent of children are seropositive to H3N2 and 20 percent are still seronegative to H3N2. And something on the order of 50 percent were seronegative to H1N1.

So a minority of children by age five would need two doses using that kind of analysis.

But remember, this depends on the era in which we live. And right now we're primarily in a H3N2 era, and it's going to be different in the future, and we don't know how to anticipate that.

CHAIRMAN DAUM: Five Committee hands shot up while the slide was there, and I really want to move to the question. But we will recognize these five people if their question specifically concern the new data that have been shown. So we'll start with Dr. Stephens.

DR. STEPHENS: My question has to do with the column under efficacy the vaccine for H1N1. And it looks like -- could you just clarify that those efficacy -- how those efficacy data were calculated in reference to what looks like a very nice serological response, yet a rather weak efficacy if I'm interpreting that correctly?

DR. MENDELMAN: The efficacy vaccine column is the seroresponse column. So it was one of the lots that was used in trial AV006. In this study it was just used for immunogenicity and safety.

CHAIRMAN DAUM: Dr. Schild?

DR. SCHILD: That's the same question, really.

CHAIRMAN DAUM: Thank you.

DR. SCHILD: The efficacy vaccine for H1N1 was 42 percent sero-conversion, which was significantly different from lots 1, 2 or 3. Is there any explanation for that?

DR. MENDELMAN: You picked out the difference. The H1N1 and the efficacy vaccine is A/Texas. And the H1N1 in the three consistency lots is A/Shenzhen. So it's a different H1N1 strain.

The match is the H3N2 and the B on this table, but the strains had not changed.

CHAIRMAN DAUM: Drs. Kohl, Myers and Goldberg. This issue only. Mr. Kohl is out. Dr. Myers.

DR. MYERS: Dr. Griffin asked my question.

CHAIRMAN DAUM: Dr. Goldberg? Wow. Okay. We are that heady moment when we can begin to actually address the first question. And, Dixie, you of course are in the seat of distinction up there. Everyone in the Committee is grateful to you as evidenced by the affection Dr. Kohl is showing for you.

Would you begin our discussion of question one, please?

DR. SNIDER: Thank you, Dr. Daum.

CHAIRMAN DAUM: Welcome, sir.

DR. SNIDER: With regard to the subpart (a) the pediatric and adolescent population data, I think that we have data from two influenza seasons in this age group, which demonstrate at least four the strains that we're circulating at the time, a reasonable degree of efficacy with at least two doses. I don't think that we have enough data to be able to feel comfortable about one dose, although it's still an open question even though we were looking at the sero-conversion rates and trying to make some sense of

them, some of the other data that was presented to us suggested that perhaps the sero-conversion rates are not really that good a measure, at least of the internasally administered vaccine.

But the number of participants in the one dose group is much smaller, so the evidence for the two dose versus the one dose is much stronger, but it would nice to be able to find out subsequently how much protection one would get from one dose. Obviously, that has economic, logistic and many other implications.

With regard to that population it's already been noted that we don't have an even distribution of participants throughout that whole population. And particularly there's been concern with the youngest part of that population. And therefore, the efficacy data for that particular part of the population is not as strong as it would be for some of the older groups that are included.

The timing of doses I think we didn't as much clarification on that point as we might have liked, and I come away really not knowing what the optimal interval is between dosing. But, obviously, we do have some efficacy data based on the dosing that was used. And we don't know if that's optimal or not,

but it certainly appears to be satisfactory in that it, for at least the years examined, we saw a fairly high level of efficacy.

With regard to the adult populations of part (b), the adult population information we have is primarily data on I guess what we might call effectiveness in the sense that we don't have the culture monitoring data in this population. Nevertheless, as Kristin Nichol pointed out to us and many other people have emphasized, there was a substantial impact on influenza like illness in the adult populations. We have to recognize, though, that his is a new disease every year and we have two year data for the kids and one year data for the adults.

I think the challenge study data, obviously, everyone has said and I'll just repeat, that it would be nice to have field challenge data for H1N1, but we don't and there's good reasons we don't have the data for the time period the studies were done. And the numbers of the subject, although relatively small, still with an attack rate, as I recall, of approximately 45 to 50 percent in placebo demonstrated a substantial protective effect against H1N1.

So, I would like to see larger numbers,

but don't have serious questions about efficacy against H1N1. So if the data are not adequate for specific age ranges, please discuss what additional data should be requested. Obviously, I've alluded to this along, but we'd like to see more data in the younger age groups. It would be nice to see data for, at least in my mind, the age groups that weren't included that are not being requested here. Because I think there may be a role eventually for FluMist and enhancing immune responsiveness in the elderly. We may in the elderly and immunocompromised populations have a benefit from this vaccine. So ultimately I'd like to see that. But that's not an issue relevant to our advice about licensure for the indications that the manufacturer is seeking right now.

I think I'll just stop at that point and let other people add.

CHAIRMAN DAUM: Okay. I'm happy to let you off the hook, Dixie, but first you have to answer the question with a word, and that is are the data adequate to support the efficacy of FluMist in (a) pediatric adolescent population and (b) the adult population. And all your comments have been on the money and noted, and so we just need a yes or no.

DR. SNIDER: The data support efficacy.

CHAIRMAN DAUM: That would be mean yes?

DR. SNIDER: Yes.

CHAIRMAN DAUM: Good. Thank you.

Dr. Kohl?

DR. SNIDER: I won't say how much or how strongly they do.

CHAIRMAN DAUM: No, I understand. You know, the comments are helpful and are noted and recorded. But we still need a vote on this one.

Dr. Kohl, please?

Thank you, Dr. Snider. I know that wasn't easy.

DR. KOHL: Thank you, Dr. Snider. I really missed you at the last meeting.

I am very comfortable with the efficacy of this vaccine as administered both for the pediatric population and for the adult population. So I would vote, yes, yes without reservations for efficacy.

What I would like is pertinent to the second part of this question, and I think we very much need studies to determine whether one dose is as adequate as two doses. And I'm hopeful that even though this might be contra to the economic interests of the company, which obviously would benefit from a two dose regime more than a one dose regime, that we

will see those studies going ahead rapidly.

I am also not at all sure what the age range is for this two dose necessity, if it will prove to exist. So, again, that reenforces the need for a two dose versus one dose study.

And I'll stop there.

CHAIRMAN DAUM: I thank you, sir.

Dr. Faggett, you're up.

DR. FAGGETT: Yes. I think the data do support efficacy of this vaccine for the pediatric and adult adolescent population, but I would say from 2 to 17 I'm not real sure about the one under two. But I think, you know, as a practicing pediatrician we really are very excited about the possibility of having effective relatively safe vaccine with ease of administration. And we think this is going to really help us close the gap in disparity of flu immunizations in our vulnerable and underimmunized population.

So, it does really look effective from the data.

For the adult population, again, I agree with the first two speakers. It does appear to be effective from efficacy data presented.

I have to defer to some of the other

experts relative to the efficacy against H1N1 influenza strains. I didn't really think we had enough data to come to a conclusion on that one.

And I do agree that we need lot more information about the patients, especially the younger patient, the 12 to 24 month old.

The point about one or two doses, again, I think we do need more data to really make a decision on that.

So my answers are yes, yes.

CHAIRMAN DAUM: Thank you, Dr. Faggett.

Dr. Goldberg?

DR. GOLDBERG: Okay. Let me take them one at a time.

CHAIRMAN DAUM: Can you pull the microphone real close to you? It has a longer cord. Great. Thanks.

DR. GOLDBERG: A, yes. That said, I think there are a need for additional data, and I'll come back to that.

And B, yes, but again additional data.

The challenge studies, I believe, you need additional data for the challenge studies. I think the data are promising, look okay, but they're very weak.

For the pediatrics indication, it seems to me that you need a one dose versus two dose study. And within that if you're going to propose two doses, you do need to study the optimal regiment in a controlled way.

There's very inadequate data regarding the repeated annual dosing. The second data is limited and beyond that it's very limited, and it seems to me you have to do some studies and I'm not sure sitting here what the right designs are, but you do need some studies to study the effective repeated annual dosing. This is a new way of dealing with children and you're vaccinating them every year, and I think there are a lot of issues that are raised by that.

You haven't presented any combination data here except for a little bit in passing during the discussion with the other vaccines that are given to the 12 and 15 month old, and I think you need some studies of that issue. And I think you can probably combine these into the same study, that that takes care of that.

And then in adults, your indication is for healthy adults 18 to 64. That's a very difficult thing to implement. What is the definition of healthy and you need to have a plan to deal with that. You

need to have a plan to expand this out to reasonably healthy and other levels of health and health changes. So you're proposing a live vaccine yearly, and I think this needs to be addressed. And, again, your challenge data in the adults are weak.

And that's it, I'll stop.

CHAIRMAN DAUM: Thank you, Dr. Goldberg.

Before we call on Ms. Fisher, I'd like to implore everyone in the room to help us. That is to say cellphones, please, turned off. Beepers please turned off and flash please not use. Those are fairly simple rules and I hope they're simple and will help the Committee a lot concentrating on what is a very difficult task, as you can see.

Thank you for your cooperation.

Ms. Fisher?

MS. FISHER: I can appreciate the complexity of trying to gather data for a new vaccine that would be used by virtually all age groups from infants to the elderly, and it's an enormous task.

FluMist appears to be effective in healthy children and adults, even though there are low levels of serum antibody, but I'm troubled by the lack of understanding of the biological mechanism for immunity and the implications of a low H1N1 antibody response

compared to the other strains.

This, together with the increased incidents of influenza like illness including fever after flu misvaccination with compared to placebo, especially after the first dose, leads me to want to see more carefully collected efficacy data, especially in children under five years old, because these children are receiving 37 doses of 11 vaccines during that time period, and many of them are presenting at the time of vaccine with a coinciding viral or bacterial infection. And I don't think this efficacy data is adequate to reflect the real environment in which this vaccine will be given to children. So, I would like to see at least 3,000 more children under the age of 5 with particular emphasis on those under age 2 evaluated with one or two doses over a period of four years to measure for antibody responses to the different strains for instance of influenza like illness and viral shedding with particular attention paid to whether there are individual genetic or other biological factors such as acute or chronic illness which contribute to variations of the antibody response, efficacy and the general health of the children over time after repeated use of this vaccine.

It's very difficult to answer the question

yes or no. I would say that it's very encouraging that it looks efficacious but for me without the longer term data, especially in the young children, I cannot vote today to say yes on efficacy. And so, I just, I'm going to have to say no.

CHAIRMAN DAUM: That's on both (a) and (b)?

MS. FISHER: I would like to see more data over time on adults also. That's no on both.

CHAIRMAN DAUM: Thank you, Ms. Fisher.

Dr. Stephens, please.

DR. STEPHENS: I sometimes feel like I've come to a house closing and I've done my walk through and found that all the rooms aren't finished and I'm being asked to close anyway.

This vaccine has been shown to be effective and efficacious, certainly in the 15 to 71 month old group. The 06 study clearly showed that, in my view.

My real concern is this indication for the vaccine between 1 and 15 months, an area we've discussed at some length. and I think the issue of concomitant vaccines in that group has not been fully explored.

CHAIRMAN DAUM: One and 15 years.

DR. STEPHENS: I'm sorry. Between one year -- 12 to 15 months, excuse me, is my concern for the efficacy of that group where concomitant vaccines are concerned.

I also have, because the data is limited and because of the issues pointed out earlier about what is a healthy adult, especially those in the 50 to 64 range, I think the data is quite limited in that particular population, although I do think this is, obviously, an important vaccine and an important breakthrough.

So I have mixed feelings. My major concern has to do with the issue of efficacy in the young children, where I don't think that data in the 12 to 15 month old group is there.

CHAIRMAN DAUM: I'm not quite clear on where to categorize you, Dr. Stephens?

DR. STEPHENS: Well, I think that if part (a) was 15 months to 17 years of age, I would vote yes. If it remains 1 to 17 years, I will vote no. And in terms of the healthy adult population, part B, I would vote yes.

CHAIRMAN DAUM: Dr. Stephens, I thank you.

Dr. Griffin?

DR. GRIFFIN: I think that I feel very

much the same way Dr. Stephens does, except I might extend it up to two years of age discomfort level between 1 and 2 years of age.

We do have data in that older, between 1 and 2 months of age -- or 1 and 2 years of age group that I think does support efficacy. And so I think that it is efficacious in 15 months old to 17 years of age, but I don't know that we know that it's efficacious when it's used the way that it will be used, which is in conjunction with all the other vaccines that are being given during that period, primarily between 12 and 15 months, but not everybody gets their doses on schedule.

So if I were being asked to vote for the, and I am, 1 to 17 years, I have to say no. If it were 2 to 17 years, I'd say yes.

As far as the more data, the one to two dose schedule, as a number of other people have said, and I've commented on, I just don't think we have the data for either knowing what age that should be implemented or if it's even necessary to have two dose.

I vote yes on the (b) population although I, like everybody else, would like more data.

CHAIRMAN DAUM: And you'll have a chance