time?

DR. MINK: I'm not allowed to speculate. Actually, we can ask the sponsor if they'd like to comment if there was a difference in Houston compared to the other sites.

CHAIRMAN DAUM: Could we get this mike on, please?

DR. BELSHE: I just wanted to comment, actually, as well, on slide 18, but in that particular analysis, only ill subjects were cultured, whether they were in the vaccine or placebo group and then we divided the ill vaccinated subjects to whether they had positive cultures or negative cultures and concluded that the vaccine virus shedding was associated with illness but that's a self-fulfilling prophecy, because only ill subjects were cultured.

And I think that a better way to -- if you shed more virus, are you more likely to have illness associated with FluMist™? We've addressed this formally in the NIE studies using monovalent vaccine in which all subjects were cultured on a daily basis and the virus shedding pattern described and in fact, in one study, I believe Ed Anderson's study of H3N2 vaccine we can show a decrease in symptoms associated with a virus setting suggesting that there were inner

current things actually suppressing replication of the vaccine virus. And so I would suggest what this analysis really needs is to look at the positive culture rate in a similar cohort because this is only 20 percent of the children shedding and I would expect on any given day that 50 percent would be shedding virus in the vaccine group and you're actually showing a decrease in shedding here.

DR. MINK: Actually, I think that's probably a different analysis. What this was looking at was the subjects who were cultured who were ill in the first 14 days, which was not specified in the protocol. And in these groups what we looked at with the assistance of the sponsor was of those subjects who were ill with cold-adapted virus versus subjects who were ill that were culture negative potentially due to other viruses, we saw a difference in the illness profile. These numbers are small and they haven't been statistically analyzed to see if the differences are significant.

CHAIRMAN DAUM: Thank you very much. Dr. Eickhoff.

DR. MINK: I don't think I answered Dr. Eickhoff's question about what was unique.

CHAIRMAN DAUM: Does anyone want to

attempt to answer that question?

DR. MENDELMAN: Paul Mendelman. I think the -- if we could put a slide up the --

DR. MINK: My side?

DR. MENDELMAN: One that we have on the computer here.

DR. MINK: Okay.

DR. MENDELMAN: The data Dr. Mink is quoting is correct and we did this analysis at CBER's request. It's important to note that there may be case ascertainment bias and it's a non-randomized comparison because you're looking at children who are all FluMist™ recipients and a subset who are sick, cultured and you're looking at the positive versus the negative. In the randomized comparison shown on this slide, would be all the 116 plus children in the 2 to 1 randomization, so it's the randomized comparison.

Whatever brought them into the clinic at the investigator sites agreed most of the cultures were done at Houston but there were other representative sites in this analysis, so looking at the 77 FluMist™ recipients on this slide compared to the 38 placebo recipients and if we look down the case definitions that CBER asked us to do or looking at the reactogenicity that were collected, you can see that

the differences here noted on the culture positive versus culture negative FluMist™ recipients really are significantly reduced in this analysis which was also presented to the agency. So I think that's one way the committee to clarify what was going on in the 14 days after vaccination at these sites.

DR. MINK: Again, I think that this is a little bit different because these are 78 FluMist™ and as I stated at least 66 of those were after day 11 and there's probably a temporal difference and that the first 14 days post was when there were more subjects that were culture positive for cold-adapted influenza. But I will give you that the analysis is still ongoing.

CHAIRMAN DAUM: Dr. Eickhoff, are you comfortable with the answer here? I don't know if --

DR. EICKHOFF: No, but there may not be an immediate answer.

CHAIRMAN DAUM: Okay, thank you. Let's go on to Dr. Edwards.

DR. EDWARDS: I think one of the issues surrounding the pneumonia question is the very well-known fact that when you're hurrying to get people immunized for the influenza season that you also have a contending problem of RSV that is co-circulating at

that same time. So is there any data from the sponsor that looks at these children that had respiratory illnesses, had pneumonia for the presence of RSV?

DR. MINK: I can tell you that the AV006 began from August and went through November, so most of that enrollment and follow-up was before RSV season although subjects toward the end were entering into RSV season just, you know, based on usual circulation of RSV. However, I'm sure the sponsor has this data about what other viruses were cultured but that's not yet been submitted either. Do you guys want to comment?

DR. MENDELMAN: Paul Mendelman. The investigator sites routine cultured on RMK cells and that would have been grown in order to optimize the growth of influenza. Certain cell lines that are more permissive to RSV were not inoculated and there wasn't a question of this study what other viruses, respiratory viruses might be present. It was really trying to answer the question about influenza efficacy and trying to limit the amount of reagents that the investigators were needing to do and the number of cultures they needed to do.

DR. MINK: So like we just have seasonality, I guess.

CHAIRMAN DAUM: Dr. Katz and Ms. Fisher.

DR. KATZ: Dr. Mink, you cited one study of HIV infected adults.

DR. MINK: Right.

DR. KATZ: And I really had three questions really. One, how were they selected as far as where they were in their illness, two, did anyone study their antibody response and three, you said that they had no increase in virus load and I wonder when that was assayed.

DR. MINK: Okay, it is actually a very complex thoughtful study design in that the enrollment was staged at initially subjects who had CD4 counts greater than 500 who had been clinically well and either not on anti-retroviral therapy or on a stable regiment for at least six weeks were enrolled and the next phase the CD4 count was lowered to 200. I'm sorry, I don't remember that ends in each of those phases.

The viral load was followed actually, I think -- I can't remember and hopefully the sponsor can help me out, at zero and an interim period of either 7 or 12 days, at 28 days, at 3 months, at 6 months. Even though it's a small study, it was comprehensive.

DR. KATZ: And did they demonstrate any rise in antibody?

DR. MINK: Serology was performed on these subjects. I don't remember if it's in their briefing documents. If it's not, if the sponsor can't provide it to you, I can provide it to you. And actually there wasn't a noticeable difference between the HIV positive and the HIV negative subjects for the immune responses for the different sero-types.

DR. KATZ: Thank you.

CHAIRMAN DAUM: Ms. Fisher, then Dr. Edwards.

MS. FISHER: Thank you for a very excellent presentation. You emphasized several times that the FDA's review is ongoing, particularly for evaluation of pneumonia and bronchitis after vaccination, the increased reactions in asthmatics. Does the FDA staff feel comfortable about the amount of data they have so far in terms of our voting on this issue tomorrow, or do you believe we need more information?

CHAIRMAN DAUM: Can I interrupt as a matter of order here? It seems to me that FDA is asking our advice on that very question. So to ask them to advise us to advise them doesn't compute.

MS. FISHER: No, I think it's very important when you have a presentation by industry and presentation by FDA staff and when you have several times being stated that the FDA review is ongoing, that we need to know whether or not there's enough data here in their opinion, in their expert opinion for us to be voting tomorrow.

DR. MINK: I can give you an easy answer. We are required to discuss and BLAs with the advisory committee and there on a 10-month clock. So we come to you in July because of our 10-month clock and we are mandated to discuss products with you before a complete response is provided to the sponsor.

MS. FISHER: Perhaps I can clarify.

CHAIRMAN DAUM: Dr. Geber, do you wish to comment on this question?

DR. GEBER: Yes. I think that we have received -- we received the BLA in October of last year and we have by and large completed our review of those data that were received at that time. The sponsor has requested that we present that information to you today and we're doing so. We have subsequently received additional information from the sponsor. Some of those data include the Kaiser Permanente study which Dr. Mink eluded to were submitted to us at the

end of April in an unblinded fashion and so the review of those data from our perspective are ongoing.

And the sponsor has committed to submitting a complete data set from that study. In discussing the respiratory events that Dr. Mink has discussed, what we say about our review being ongoing that in the study reports that we've received, we did not have summaries of pneumonias, of bronchitis, of bronchiolitis. So in order for us to analyze this data, we've had to go back and search the data bases.

And it's a multitude of factors that lead us to the statement that our review is ongoing. I think that's where we're at.

MS. FISHER: Thank you.

CHAIRMAN DAUM: Thank you very much. Dr. Edwards is next.

DR EDWARDS: Could you comment a little bit on the cultures that were taken within the first 14 days, those were performed at the laboratories of the investigators and then were the investigators told what was isolated which would subsequently unblind them or did they all go to a central place or how was that managed?

DR. MINK: That's correct, they were performed at the site and then sent off to Aviron labs

for confirmation.

CHAIRMAN DAUM: Dr. Stephens.

DR. STEPHENS: This is a specific question regarding AV014, which is the bridging study. And you have a statement in your handout that says that the study did not achieve the goal of demonstrating equivalence between the two manufacturing facilities. Can you comment on that statement?

DR. MINK: You should have received an amended handout. Those criteria of 20 percent were accepted by CBER.

DR. GEBER: There was some confusion as to whether we had accepted the 20 percent point estimate or whether we accepted the confidence interval but the sponsor has pointed out to us and correctly so that what they had proposed was a point estimate and that apparently is what we accepted.

CHAIRMAN DAUM: Dr. Snider?

DR. SNIDER: A couple of questions that perhaps can't be satisfactorily answered but I'll ask them anyway. One has to do with the fact that this vaccine, I guess not in trivalent form but in monovalent and/or bivalent form was administered at one time as drops as opposed to the nasal spray. And I was wondering if there had been any observations at

that time of lower respiratory infections and -- in the same 21-day interval after administration.

And the other is whether in earlier studies of the vaccine, whether there had been a different control, normal saline or some non-protein containing substance that was administered at the same time that would give us a better handle on -- because as you point out, both the placebo and the vaccine are reactogenitic. I was just wondering what baseline data there may be for getting some sense of what is caused by the vaccine with all of its constituents versus having nothing or having normal saline sprayed into your nose.

DR. MINK: Would you like to answer Aviron?

DR. MENDELMAN: Paul Mendelman. Our review of all the literature shows that all the prior studies conducted by the NIH were with egg allantoic fluid that we could review. Obviously, the importance of having a placebo controlled that visually and indistinguishable and taste, smell and every other way is important to limit a lot of bias that can go into a randomized placebo controlled trial.

So we've also used allantoic fluid for that reason. I'm sorry, Dr. Snider, what was your

first question? Oh, I remember. AV001, the very first trial conducted by Aviron with the NIH in adults looked at FluMist™ delivered by drops versus FluMist™ delivered by spray and there was no difference in the safety profile in that study or in the immune responses. The second trial conducted, AV002, with the NIH looked at drops versus spray in children, and again, no difference in the immune response and the safety profile.

And then subsequent, starting with study AV003, and on all sprayers were used.

CHAIRMAN DAUM: Thank you for clarifying. Dr. Griffin and Dr. Schild.

DR. GRIFFIN: I'm not sure who this is a question for, maybe it's for Brian Murphy or maybe it's for somebody from Aviron but I was just wondering if it was -- how much we know about the neurovirulence of these viruses. Influenza in general is not a neurovirulent virus but we are giving it intranasally and I would just be interested in knowing what kind of information we have on that question.

I notice that meningitis and encephalitis, that sort of thing were not monitored events but I assume that they would clearly have been picked, you know, as adverse events in the Kaiser study, et

cetera.

DR. MINK: They were monitored, like in the Kaiser trial, the CNS was one of the long laundry list of --

DR. GRIFFIN: I just looked through that laundry list and I didn't find it, but maybe CNS I looked for, yeah.

DR. COELINGH: I don't have much to add. I would agree with you that influenza is not either neurovirulent or neurotropic, the wild-type influenza even and for that reason we have not performed neurovirulent studies.

DR. GRIFFIN: I mean, there are neurovirulent strains for animals that are well studied. I just -- I don't have a good idea of how they fit into these categories.

DR. COELINGH: Those strains have -- we've had to passage those in animal strains multiple times in order to pick out variants that become neurovirulent so as far as I'm aware and anyone can correct me, I'm not aware of any naturally occurring neurovirulent human strains.

CHAIRMAN DAUM: Dr. Schild is next and Dr. Kohl, Edward and Eickhoff.

DR. SCHILD: The clinical effectiveness of

this vaccine is highly dose dependent it seems and I just wonder, it's well known, of course that sensitivity of egg assays or cell culture assays vary from time to time and between laboratories. I just wonder what is being done to validate and standardize those assays for infectivity. Is there actually a reference preparation that you use in every assay?

DR. GREENBERG: As was discussed earlier this morning, there is a very well validated potency assay that has high levels of reproducability.

DR. SCHILD: But does that include the use of the same material in every assay so that you could look at changes in sensitivity? Thank you.

CHAIRMAN DAUM: The answer was yes. Let the record show that Dr. Greenberg nodded his head. Dr. Kohl.

DR. KOHL: FDA, since we've heard data that there is a limited by finite risk of transmission of this virus, as shown in both the Peter Wright studies and the daycare center studies, I'm a little concerned about transmission of the virus to high risk hosts who are contacts living in families, HIV infected people, kids with immuno deficiencies, et cetera. Other than the HIV data that we've heard which are fairly healthy HIV folks, are there any

other data on high risk hosts or are there any forthcoming?

DR. MINK: For shedding in high risk subjects?

DR. KOHL: No, for serious illness in high risk subjects or unusual adverse events in high risk subjects.

DR. MINK: I think Aviron wants to answer this, too. There was also an HIV pediatric trial that has been performed. I don't know in what stage that is and there's still some asthma subjects to be evaluated. What else do you have?

DR. MENDELMAN: Paul Mendelman. You're correct. The pediatric HIV trial also, these are children infected with HIV, not AIDS subjects and the control, similar to the adult trial, were non-infected children with HIV. And those data will be available for CBER and if there's a particular question, the lead investigator, Dr. Jim King, is in the room that can address the question about either the adult HIV or the pediatric HIV trial, if there's a specific question that Dr. Daum would like addressed to Dr. King.

CHAIRMAN DAUM: Thank you, Dr. Mendelman. Dr. Edwards, please.

DR. EDWARDS: I just did want to add that there have been increasing reports from Japan about encephalitis associated with wild-type influenza strains. So I thing that that is a very reasonable question that Dr. Griffin raised.

DR. MINK: In the data base there was one diagnosis of aseptic meningitis in AV012, the Texas community trial. In the Kaiser study, I believe it was on the list of queries and there wasn't an increase in CNS events to the data base so far. If you want to add more, go for it.

DR. BELSHE: We did, as part of potentially influenza related rare events look at encephalitis and aseptic meningitis and did not identify any case of either in the interim analysis or in the final data set.

CHAIRMAN DAUM: Thank you. We're going to go on for about five more minutes here. We'll have time tomorrow morning to return to things that people would like to reraise and we'll have both FDA and the sponsor here to provide additional clarification. So I have Dr. Eickhoff, Steinhoff, Daum and Cox. Dr. Eickhoff, please.

DR. EICKHOFF: My query has been answered.

CHAIRMAN DAUM: Dr. Steinhoff.

DR. STEINHOFF: One of the things we've been hearing about and one of the questions we're supposed to answer is the issue of reassortants and reversion in these viruses. And listening today we've seen lots of information about examining phenotype and genotype of the seed viruses and of the reassortants that have been tested. I may have missed something but I don't think I've seen any data on more than there was some information about phenotyping of the viruses that come out of the vaccinated kids. We've seen a fair amount of information. These kids do shed virus. They shed it up to 7 to 8 days, may or may not be associated with symptoms.

We are usually told that it's phenotypically stable. But it would seem to me that if the data is available, we should get that information on the characterization of the viruses from vaccinated kids. We've seen some. I'm not saying I haven't seen any. We've seen some data but here's what I'm curious about. If you take 100 kids or 1,000 kids and give them this virus and if half of them shed, what do we know about the viruses that they're shedding? I would guess there must be some finite rate of change. It may be the same as the master strain, but it would seem to me this would be

important data to have, to be able to characterize the variability of the vaccine strains.

CHAIRMAN DAUM: It's a thoughtful comment, Mark, and it goes very nicely with what we're going to be discussing tomorrow morning. We'll see if Dr. Mink wants to comment on it from the point of view of the FDA's perspective this afternoon.

DR. MINK: Good idea.

CHAIRMAN DAUM: Thank you very much.

DR. STEINHOFF: The point is though, there may not be data right now, so that we need to think about what kind of data do we want or are we interested in.

CHAIRMAN DAUM: And I think I would like you to reraise this tomorrow at the right moment. I think it's an important point. Dr. Greenberg.

DR. GREENBERG: I think the sponsor will be able to help in that discussion tomorrow morning.

CHAIRMAN DAUM: We will be grateful for that help. Dr. Mink, I'd like to ask you a question that shows how little I know about influenza but you indicate that there were several kinds of adverse events that were biologically plausible and mentioned abdominal pain among those. I need a little bit of help with that. How does influenza cause abdominal

pain? What kind of abdominal pain are we talking about?

DR. MINK: Actually, the biological plausibility was assigned by the sponsor for those categories. You could postulate and this is postulation, that the virus that's sprayed in the nose could be swallowed and potentially you could have some sort of response that way but natural influenza, a lot of times the kids will have abdominal discomfort or GI discomfort associated with the illness.

CHAIRMAN DAUM: Dr. Greenberg, do you want to speak to this very issue?

DR. GREENBERG: I think the biologic plausibility was based on the well documented association of wild-type influenza with abdominal pain. So it was sort of biologic epidemiologic plausibility as opposed to strict pathophysiologic plausibility.

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

DR. COX: Yeah, I think this is actually more of a comment than it is a question. I don't quite know how to formulate the question. But I keep going back to the pneumonias that might possibly be associated with FluMist™ administration and back to

the particle size and knowing that the small particles could possibly be deposited in the lungs, and obviously, we know that the live attenuated vaccine should not replicate in the lungs so therefore, you should not -- because it's temperature sensitive, so you should not have disease caused but I'm just interested in what comments the sponsor might have with regard to these comments.

CHAIRMAN DAUM: All right, it's late in the day. Let's hear your comments, sir.

DR. MENDELMAN: Paul Mendelman. The one case that Dr. Mink has talked about is when cold-adapted vaccine was isolated from a child on day 3 after vaccination, a Type A virus vaccine and on day 8 was a Type B virus. On day 3 the child was see when a culture was taken and by chest x-ray, and by the documentation and the records that are under review, the investigator noted that the chest x-ray showed a consolidated bacterial process pneumonia.

And I think that my estimation on that one, Dr. Cox, is that the child was dosed with FluMist™, so likely the child is going to be culture positive for FluMist™ if you culture the child and happen to have another co-infection that was brewing prior to the vaccination, I think that from a

pediatric infectious disease is to rapid to have a consolidated pneumonia. If Dr. Daum, I could have a slide put up to maybe clarify the pneumonia question for Dr. Cox and for Dr. Snider.

The comparison in an open label trial, Dr. Glezen's trial, a community protection trial in Temple, Texas and this was brought up by Dr. Mink, these are data that have not been submitted to the agency but in part have been presented at national meetings. And this is year 1 and year 2 of the trial for the children and in this analysis looking at medically attended acute respiratory illness, the child is his or her own control. So this is looking at 14 days after being vaccinated, compared to the reference period, which is in the data base states prior to enrollment in the study, and day 15 and beyond, so it's a rolling type of analysis that many of you are aware of, then I guess I would just show you the last line, LRI on the slide in year 1 and year 2 and the relative risk column on the second to last column, actually there's a reduction. The relative risk is .5 and .6.

Comparing the child to himself, albeit the bias is in a non-placebo controlled trial, but given that we're probing placebo controlled trials for is it

egg allantoic fluid reactogenitic, here is the kind of trial one could do without a placebo control and there does not appear to be pneumonia or bronchitis any other lower respiratory events excluding asthma events and albeit the agency hasn't seen these for their own analysis.

CHAIRMAN DAUM: Thank you very much, Dr. Mendelman. Dr. Greenberg, the last word.

DR. GREENBERG: I just wanted to clarify very briefly the issue of lung deposition of infectious agents and particle size. I think, Dr. Daum, you probably remember the publications better than I do but I had forgotten but actually Dr. Gordon Douglas is in the audience reminded me that the association of increased infectivity and infection $dose_{50}$ with particle size is really carried out with a specific nebulizer that made 1 micron particles and that's what the data is.

DR. MINK: Actually, can I have one last comment?

CHAIRMAN DAUM: Yes.

DR. MINK: Remember that you get pneumonia after influenza with it only ever getting in your nasopharynx.

CHAIRMAN DAUM: Okay, now we have Dr.

Geber stepping up. This will be the last.

DR. GEBER: You know, I think the FDA has presented data on pneumonia that we have not -- we've received case report forms within the last week, so we haven't reviewed them all. We have some suggestion of a point estimate relative risk being increased in the first year of 006 but the confidence interval overlaps 1 and so we are just presenting the data as we know them now and we have not finished our review of 019, but you have heard from the sponsor that no increase was seen in their review of those data and I think that that's where we're at and that's the only point we're trying to make.

CHAIRMAN DAUM: Thank you, Dr. Geber. Committee members, we are not at all sure that this room will be locked overnight, so we ask you to take your materials with you. We will reassemble promptly tomorrow morning at 8:30.

(Whereupon, at 5;41 p.m. the above-entitled matter recessed to reconvene at 8:30 a.m. on July 27, 2001.)

CERTIFICATE

This is to certify that the foregoing transcript

in the matter of: VACCINES AND RELATED BIOLOGICAL PRODUCTS ADVISORY COMMITTEE

Before: CENTER FOR BIOLOGICS AND RESEARCH

Date: THURSDAY, JULY 26, 2001

Place: GAITHERSBURG, MARYLAND

represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.

Rebecca Davis