there's no statistical difference between FluMist™ and placebo following the second dose of FluMist™. The next slide presents an analysis that we conducted with a complex of these illness events. The analysis uses the Center for Disease Control influenza like illness definition which is published in the literature in the MMWR and other publications and used the definition of a temperature of greater than or equal to 100 degrees Fahrenheit with cough or sore throat.

And there was no difference after dose 1 or dose 2 in the CDCILI definition. As we know, fever is the hallmark of influenza and systematically based on the temperature recordings by the parent/guardians, we evaluated these temperatures and the one temperature that's statistically significant higher in the FluMist™ recipients which is about four percent significant after the first dose, not after the second dose, and the higher temperatures are not significantly -- there's on significant difference after dose 1 or dose 2 in the higher temperatures evaluated.

The next slide presents the medication use during the reactogenicity period are recorded by the parent/guardian. There was one event or one

medication used category antipyretics/analgesics which is statistically significant, the difference of about five percent between FluMist™ and placebo recipients. It's not significantly different after the second dose. The other three categories, antibiotics, antihistamines, beta agonist use, whether it was dose 1 or dose 2, there is no significant difference.

The next slide presents the data for numbers of children dosed after and/or repetitive dosing and subsequent seasons; 4,771 children had been dosed for a second season, nearly 2,000 for a third season and 549 children have been evaluated over four consecutive seasons showed under initially in the AV006 efficacy trial. It was a two-year trial and then followed for an open label study in year 3, revaccination and 4 purposely to evaluate safety on repetitive dosing.

The next slide presents the reactogenicity profile across the four years. This is runny nose, nasal congestion which was collected in children as a single event. This is dose 1 and year 1 followed by the subsequent seasons where it's reduced. There was no pattern of increasing reactogenicity for any of the events evaluated in the subsequent seasons in these children.

The next slide presents selected events based on what you've heard from Dr. Black in the Kaiser trial and the conducted with Dr. Shinefield and also our own evaluations. These are placebo controlled trials that did not include the Kaiser trial. The Kaiser trial was medically attended events within 42 days. So they had to seek medical attention to be on the data base tapes. These are what the parent dealt with in the reactogenicity period and then recorded by them.

For conjunctivitis, the incidents rate is low and similar between the FluMist™ and the placebo recipients after dose 1 or dose 2 in the placebo controlled trials. For abdominal pain, in the FluMist™ recipients, 1.5 percent compared to .7 percent in the placebo recipients and .8 versus .4 percent after the second dose. I'll discuss this further on a subsequent slide but let me just note, lower respiratory illness, similar incidents after either dose in the two treatment groups which were not significant and otitis media, which was similar and not significant after either dose.

For lower respiratory illness, the categories that were included in there were pneumonia, bronchitis, bronchiolitis, asthma, wheezing, croup, et

cetera. I will note that on abdominal pain, there was one study noted here, Study AV006 where we did have higher incidents of abdominal pain in the vaccinees compared to the placebo recipients. Next slide, please.

Shown here is the 1.5 versus .7 percent. The age in these children with abdominal pain is identical to what you'd expect for the children enrolled in this age group. They were approximately four to five years of age. The abdominal pain was two to three days. Three of the 25 children's parents sought medical attention for the abdominal pain. Where severity was measured, most were mild. One was noted to be severe and this was a serious adverse event. The child developed the abdominal pain on day 9 after vaccination, was admitted for an overnight stay in the hospital and was discharged the next day without abdominal pain.

Most of these abdominal pains are recorded on the diary card as tummy ache or stomach ache by the parent. In evaluating the data that you heard from Dr. Black on the next slide we wanted to do an analysis of appendicitis. As you heard from Dr. Black there were two cases that went to appendectomy of the 6,473 vaccinees. That incident is 1.5 per 10,000

person months. It's lower if we remove the child who had a histologically normal appendix and it's even lower than that if we remove the child who had appendiceal abscess who had abdominal pain prior to being dosed with FluMist™.

But we also looked at our other large HMO trial being conducted by the Baylor College of Medicine group under an NIH grant which has currently been a three-year trial. There are no cases of appendicitis among over 4,000 individuals in the first year of that trial. There was one in the over 5,000 vaccinated children in the second year of that trial, but there were three in the third year of that trial in 5,000 vaccinees. If we total those numbers at six, then we see that the incidents rate here is 1.3. Just to note the time sequence on these cases, that the appendiceal abscess which the dosing was on day -- the diagnosis and hospitalization was day 11 after dosing.

The event in year 1 in Texas on day 12. The other four events that occurred in the Texas trial of appendicitis occurred on day 30 or beyond after vaccination which would be outside biologic plausibility and again this trial is not a placebo-controlled trial, it's open-label. So we took published literature that we could find and local data

from both Northern California Kaiser and Scott & White HMO controlled communities in Temple, Texas. You can see the rate incidents is between .6 and 1.2 which is consistent with the overall 1.3 including all six cases.

The next slide presents data specifically on pneumonia in the Kaiser trial -- no, sorry, I'm off a slide. This is data on AV006, the two years of the trial on pneumonia within 42 days of vaccination and presents those pneumonia reported when -- day 0 to 10 based on the AE case report form from the parent filling out the diary. There were four cases in FluMist™ and none in the placebo group. These were not statistically different. In the second dose, the split was 01 but then the 11 to 42 days on these illness events report forms which you'll hear from Dr. Belshe is how we surveyed the children for influenza like illness to obtain a culture. There were eight events and three events after the first dose in the placebo group. The total 1.1 percent and .6 percent and .4 versus .7 percent after the second dose.

The next slide, please. Another comment on the pneumonia, that several of these pneumonia events upon review of the case records and noted in the briefing package from the FDA are still under

review by the FDA, several of these children, three, had pre-existing symptoms, including cough prior to vaccination with FluMist™. The data from the Kaiser trial on pneumonia and it wasn't presented to you by Dr. Black, is it wasn't increased and it wasn't decreased, but we can look at this placebo controlled trial to look at the incidents rate; 14 cases of pneumonia among the 6,000 vaccinees, 10 among the 3,000 placebo recipients for a relative risk that's .7, that's not statistically different and based on the final data analysis set just recently conducted, these numbers are 28 and 17, so the increase is concordant with the -- in both groups the relative risk is .82 and therefore, remains non-significant.

The next slide is a change from talking about these post-vaccination events that have occurred to data that has been generated on transmission, which is important to understand and has been noted in the briefing document. In November 1998 Dr. Peter Wright presented data different than what Dr. Murphy presented on the published data with Dr. Wright and himself. In the day care setting where transmission didn't occur, Dr. Wright noted to the committee that there were two children among 40 placebo recipients that he noted to the committee were potential placebo

recipients that had received vaccine virus and were shedding that virus. He also noted that these two children, based on their serology did not seroconvert to serum HAI and that these 40 children were exposed to over 100 children who were vaccinees and approximately 80 percent of those vaccinees shed in that daycare setting at Vanderbilt.

Now, as was noted earlier by Dr. Murphy, transmission may be expected to occur at a very low rate. In the trial conducted by Wyeth-Lederle vaccines is noted here. These are children 8 to 36 months of age, which would be very young seronegative children in a daycare setting in daycare groups. This was a double blind, placebo controlled trial, randomized one to one. Ninety-eight children received FluMist™ and 99 who were atomized received placebo and nasal cultures obtained systematically three times per week for the following three weeks.

And the next slide presents the data from this study. Eighty percent of the vaccinees showed vaccine virus. One placebo child showed the Type B vaccine virus on a signal day, day 15, during the 21-day period and this child was exposed to two vaccinees in their daycare group who shed vaccine virus Type B on day 7. The symptoms in this child were similar to

other participants in the trial regardless of whether they were FluMist™ or placebo mist recipients and the vaccine virus retained the cold-adapted and the temperature sensitive phenotype.

The calculated transmission attack rate is 1.75 percent and with an upper bound on the confidence interval of 8 percent and the transmission probability is .9 percent. In conclusion on the next slide, FluMist™ was safe and well tolerated in children 1 to 17 years of age, over 30,000 doses have been administered to over 18,000 healthy children. There were mild self-limited reactogenicity events observed and a low risk of other adverse events.

Thank you.

CHAIRMAN DAUM: Thank you very much, Dr. Mendelman. We will take advantage of this opportunity now to invite committee discussion of the data you've been hearing for the last 49 minutes. Dr. Kohl?

DR. KOHL: A question and a comment, Steve -- first of all, I enjoyed the presentations from everybody. Steve, in any of the children with conjunctivitis, were viral cultures obtained by chance?

DR. BLACK: No.

DR. KOHL: No. So we don't know if that's

an irritative phenomenon or an infectious phenomenon.

DR. BLACK: No, because that was not a prospectively identified outcome and wasn't identified till we looked at the data and by that time the events were passed, so we didn't have the opportunity to collect a --

DR. KOHL: I'm shocked that you guys at Kaiser don't get viral cultures on your kids with conjunctivitis. One concern I have and I'm not exactly sure how we're going to address it as a committee, but where all the adverse events results are compared to placebo and this was raised before but I want to reinforce that question again. Since the placebo was a very proteinaceous material, one would wonder if the baseline adverse events in the placebo group were really adverse events and weren't what we think of as placebo nothings sort of.

And that's just something I think we're going to have to deal with and I'm not exactly sure how we're going to deal with that.

DR. BLACK: Let me just make one comment, is we did note for conjunctivitis where we hypothesized this is by topical inoculation of rubbing the nose and then the eye which adults do often enough but kids surely do more often, that there was a

clustering of those events in the placebo group as well toward the front of the time window. So I think for that event, as distinct from the other events that we're talking about in terms of rare events, we could hypothesize that there was an irritant effect in both groups.

CHAIRMAN DAUM: Dr. Snider and Ms. Fisher and Dr. Edwards.

DR. SNIDER: Yes, in looking at the data the way you have which is appropriate, I didn't get a hint from the slide presentations of how many children actually had events, because you're, you know, counting events independently. So were there children that -- I mean, did a lot of these events tend to cluster in a smaller group of children or not?

DR. BLACK: We did not report here, but we looked at these results in two ways, the results that I reported but the binomial relative risk actually count the first event per child, so that each child only contributes one event per diagnosis to each analysis. We did also do this in another comparison using a passon (phonetic) regression that did account multiple events per child and that's in the briefing book. It really did not identify different events but the time graphs that I showed you do not account for

more than one event per child because we think that with the relatively small numbers we have here, one child with four or five visits to the doctor, could basically dominate the entire analysis and make it difficult to interpret.

CHAIRMAN DAUM: Thank you. Ms. Fisher, Dr. Edwards, Dr. Steinhoff.

MS. FISHER: One would perhaps expect that in the vaccinated group there would be a much lower rate of pneumonia and in fact, the rate was somewhat elevated in the vaccinated group but not statistically significant. But I'm interested in your dismissal of the several cases of pneumonia that occurred in the vaccinated group in children who you said had a cough or symptoms prior to vaccination when I noted that in the exclusion criteria no children with upper respiratory symptoms within one week were supposed to be vaccinated and I was wondering in the trials was it kind of not -- was the criteria not exactly adhered to or -- I mean, because writing those cases off as not related because they had symptoms prior seems to be somewhat cavalier.

DR. MENDELMAN: In general, the trials were that an acute respiratory infection within 72 hours was an exclusion criteria. The two children

that had cough, one had a cough for a month and one had a cough for a week and so those were more chronic conditions so they met the inclusion criteria because they didn't have an acute febrileness and I think we followed in general, in our protocols the recommendations for vaccinating healthy children and many children have runny nose and a cough. And we wanted to make sure there wasn't a new febrile illness at the time that they were being administered FluMist™ or placebo.

MS. FISHER: Well, in the FDA summary, though, it says that the exclusion was specifically upper respiratory symptoms within one week. So in other words, it was within 72 hours and it had to be febrile was actually the exclusion criteria?

DR. MENDELMAN: It's -- we'd have to do it per protocol, but in general it was within 72 hours, correct.

CHAIRMAN DAUM: Thank you very much. Dr. Edwards and Dr. Steinhoff.

DR. EDWARDS: Did you have the opportunity to measure serologic responses in the single patient who shed Flu B and did you think it was interesting that they only shed for a single day or was that just that they weren't shedding when they were checked

again in three days?

DR. MENDELMAN: The answer is that we did not get serology on the child and the answer is also that the next culture date, which would have been three days hence, day 18, the child was not shedding virus.

CHAIRMAN DAUM: Dr. Steinhoff?

DR. STEINHOFF: I was going to get back to the conjunctivitis question because in the two studies we heard, there was an association in one study, one apparent association, and not in the other. And it occurs to me we've already asked about other causes of conjunctivitis, the conjunctivitis can either be caused directly by the virus administered to the children or it could be irritative which you've talked about or it could be another virus and this virus somehow working together. And I don't know if you've looked at that or looked at patterns of what was circulating at the time you did the study in the two different sites. It's a complex question but --

DR. MENDELMAN: Steve, that question is for you.

DR. BLACK: Yeah, I had trouble hearing what you were saying but I'll try and answer what I heard.

DR. STEINHOFF: The real question is if you have any knowledge about other circulating causes of conjunctivitis at the same time.

DR. BLACK: Yeah, we did look and there's a backup slide on conjunctivitis I can look for here. But some of these children did have antibiotics. Yeah, let's see, it's number -- starting with number 9, I think, Yeah, okay. This is our attempt to further characterize this. Again, we -- because we were doing this after the fact, we don't -- if cultures would have been done we could have looked at them, but since there weren't we really can't but this sort of characterizes the two groups of children in terms of other diagnoses that were present, whether they had cough, whether they had other conditions.

Next slide, if I could. Yeah, and this, again, in terms of clinical features, you can see that some of the children had the conjunctivitis or evidence of conjunctivitis prior to vaccination or at least had a history of a visit within several weeks prior. They may not have had it at the time that they were vaccinated. And you can see that whether topical or systemic therapy was prescribed, was pretty similar in the two groups. I think that's really all I can say. We don't have any other information.

DR. STEINHOFF: I presume you did these studies in the summer. The immunization took place in the summer or not?

DR. BLACK: This follow-up time that we're -- you can turn that slide off. The follow-up time reporting on took place between October and the end of the year, so it's the fall.

CHAIRMAN DAUM: Thank you, Dr. Eickhoff, please and then perhaps we'll go on and hear the rest of the sponsor's presentation.

DR. EICKHOFF: A question for Dr. Mendelman; I believe it was page 4 or your fourth slide, you outlined the methods used to collect safety data on these 19,000 and some children. Could you expand on those methods just a little bit? How often were diary cards collected and filled out and how often were telephone cards made to participants and did all of the studies utilize those same identical methods of safety data collection?

DR. MENDELMAN: It varied by study. For example, in the large trial that was conducted at Northern Kaiser in 9,000 individuals, it was based solely on data base review of the Kaiser health care records, so there was no diary card. In the large study conducted by Dr. Glezen and his colleagues, in

the first year of that trial in the Scott & White Health Plan, the children are insured, everybody got a phone call on day 42 or thereafter that non-insured health plan members who came into the Scott & White Clinic and enrolled in the trial, got a postcard. They then returned the postcard. They got a registered letter.

In the second year, the health plan was very solid in terms of being able to get that data out of the data base so all the non-health plan members got a phone call and not a postcard in the year 2 of that trial. In the other trials, in general the placebo controlled all had a symptom diary card that was taken by the parent and then brought into our own data base, including the efficacy trial you'll hear about.

CHAIRMAN DAUM: Thank you very much. Okay, Dr. Cox, then Dr. Kohl, but then we're really going to go on.

DR. COX: I'd just like to go back to the pneumonia cases reported within 42 days. You have that broken down after dose 1 by says zero to 10 and 11 to 42. Was there any temporal clustering, in other words, for most of the cases around two weeks or --

DR. MENDELMAN: Okay, I think the easy one

to go to, Dr. Cox, is the backup slide from the Kaiser trial, which is slide number 15, slide number 15, slide 15, 1-5 in the back-up children's safety.

DR. BLACK: Sometimes the technology overwhelms you. This is a similar graph to the ones we talked about before and looks at the distribution of pneumonia in the two groups, the FluMist™ again in blue and the placebo in gray or whatever color that appears to you at the back of the room. As you can see, there really is not again, a consistent association or a clustering here. Perhaps there -- well, we haven't analyzed this statistically for trend but there's no evident clustering of pneumonia events.

CHAIRMAN DAUM: Thank you. Dr. Kohl.

DR. KOHL: Can you show us specific data on safety -- adverse events in the first year age, 12 months to 24 months and was there an increase in any events in that time period and how many children received vaccine at 12 to 24 months?

DR. MENDELMAN: Medically attended events?

DR. KOHL: Anything, anything you've got on that age group.

DR. MENDELMAN: In the briefing document that we provided there is a reactogenicity by age, broken by year and what you can see going from 12 to

23 months to the end of that spectrum is that decreased activity and irritability tend to decrease and then as the children maybe become more verbal, the incidents of headache and sore throat tends to increase. That's also true in the placebo group as well.

CHAIRMAN DAUM: Thank you very much. I'd like to ask the sponsor's presentation to give us the slightly less than second half of their performance and then we'll hear some more committee input. Dr. Goldberg, there are others that wish to speak and I'd really like to go on now. Is this urgent and quick.

DR. GOLDBERG: You described on the Kaiser trial and if I heard you correctly, that the surveillance for the non-insured subjects was different than for the insured members of the plan.

DR. MENDELMAN: Not in the Kaiser trial. In the Texas Scott & White trial.

DR. GOLDBERG: Did you analyze the data or just look at it descriptively to see whether there was any influence on the reporting whether you -- did you analyze it in the two stratas then of insured and non-insured patients?

DR. MENDELMAN: Right. There are analyses ongoing between the health plan and the overall clinic

population. Primarily this is a large scale trial and to evaluate serious adverse events but the investigators and Dr. Glezen is in the audience; maybe later can comment about the other analyses as they are ongoing.

CHAIRMAN DAUM: Thank you. Now we'd like to sort of go on. Dr. Mendelman, please.

DR. MENDELMAN: Thank you. The first slide again shows the historical experience; 5,348 adults were dosed with previous formulations of the 6:2 reassortants in the peer review journal articles that we reviewed, and the following slide presents the Aviron experience with FluMist™. Three thousand, nine hundred and forty-seven healthy adults received FluMist™ and 1,303 high risk adults received FluMist™. The total is 5,250, thus over 10,000 adults have received vaccine derived from the Mr. Maassab Master Donor Virus Strains.

The next slide is similar to the collection of safety for the pediatric trials except that the serious adverse events in adults were collected for day zero to 28 and in the children it was day zero to 42 and the post-vaccination reactogenicity events were collected for day zero to 7, in contrast to the children day zero to 10.

The next slide, please. The serious adverse events in healthy adults are shown on this slide, a one percent incidents in the FluMist™ recipients and a 1.4 percent incidents in the placebo recipients. I will go over some of these other events in the high risk population as we move forward in the remaining slides. Next slide, please. These were balanced as noted on that prior slide.

This slide shows the all-cause mortality in adults. There's one healthy adult who died 16 days after administration of FluMist™ from an accidental drowning. The alcohol level was .32. There were 64 deaths in adults in the VA cooperative studies program trial. All of these adults had to have chronic obstructive pulmonary disease. They all received licensed inactivated trivalent vaccine on the same day. Eleven hundred and seven received FluMist™ and 1108 received placebo. There were 34 FluMist™ recipients, 3.1 percent and 30 placebo recipients, 2.7 percent who died some time during this trial. Three deaths occurred within 28 days in the FluMist™ recipients; five deaths occurred within 28 days in the placebo recipients.

There was one considered vaccine related because of the lack of causality being provided by the

investigator. Therefore, it's considered unknown and defaults to related. that occurred 218 days after vaccination. And the three deaths that were considered vaccine related, the two at day 78 and day 158 also did not have causality, were considered unknown and were put in this category and the one on day 3 -- and all of these adults with chronic obstructive pulmonary disease obviously had respiratory events.

The next slide presents the vaccine related serious adverse events in the healthy adults. There have been one reported and again, in the VA trial there were nine for a .8 percent incidents in the vaccinees, 22 in the placebo recipients for an incident of 2 percent, these being given by the investigator prior to unblinding.

The next slide presents the demographic characteristics of adults and this is study AV009 which you'll hear the effectiveness data from Dr. Nichol. The reason to present this study is a single study, again, it's placebo controlled and provides the proper statistics and 3,041 of the 3,947 adults that received FluMist™ were in this study. The average age is 38. It's well-balanced in gender and race and ethnicity between the two treatment groups.

And the next slide presents the day zero to seven reactogenicity events, these seven events plus temperature taken. Pre-specified in the protocol was an event that was clinically significant, considered greater than 10 percent difference between FluMist™ and placebo mist. That was met for sore throat and for runny nose. Other events that were statistically significant during that time were cough, chills and tired/weak and these differences because of the large size of the trial, were statistically significant but the difference between FluMist™ and placebo were 2 to 4 percent.

The next slide presents the data for the CDC influenza-like illness definition. No difference and also temperature greater than 100 an equal number presenting with fever in the seven-day period after being dosed with FluMist™ or placebo mist in the healthy adult trial. The next slide presents the analysis on medication use. None of the four categories had a statistically significant difference, antibiotics, analgesics, antihistamines or beta agonist use.

The next slide, again to look at some of the events that we talked about in children, conjunctivitis, abdominal pain, lower respiratory

illness, these are sub-sets of lower respiratory illness as the wheezing and pneumonia and none of these are statistically significant between the two groups and neither was otitis media within that week following dosing.

The next slide in conclusion, FluMist™ was safe and well-tolerated in healthy adults 18 to 64 years of age. Three thousand nine hundred and forty-seven healthy adults have received FluMist™. There were mild self-limited reactogenicity events observed and a low risk of other adverse events. Thank you.

CHAIRMAN DAUM: How would it be if we heard from Dr. Nicol next and then had committee input after the two?

DR. NICHOL: Good afternoon. Can people hear me? I'll take that as a yes. In the next few minutes, I'm going to be presenting data on the efficacy and clinical effectiveness of Aviron's live attenuated influenza virus vaccine in healthy adults. I will be reviewing data from two trials, AV003, a trial conducted by Dr. John Treanor and colleagues that assessed the efficacy of this vaccine in a wild-type virus challenge trial. I will also discuss data from a large field trial, AV009, that was designed to assess the clinical effectiveness of this vaccine in

healthy adults.

First, AV003, the challenge trial; this was a randomized double blind placebo controlled trial. Participants were between the ages of 18 and 41 years. All had to be serosusceptible, that is have a serum HAI titer less than or equal to 1 to 8 to at least one of the wild-type viral antigens included in the challenge study, that is either to H1N1, H3N2 or to the B strain.

Randomization occurred in equal proportions; FluMist™ the trivalent inactivated vaccine or placebo. All participants received both an internasal mist as well as an inter-muscular injection. On day 28 participants were challenged with a well-matched wild-type virus. Next slide. The primary end point for this trial was protection against laboratory documented illness after challenge. Laboratory documentation was defined either as evidence of viral shedding or evidence of a four-fold serum antibody rise.

Next slide. In this schematic, we have summarized the dosing schedule for this trial. I'll figure this out soon here. Here we go. Three hundred and eighty-two healthy adults were screen for serosusceptibility. Of these 382 volunteers, 135 were

found to be serosusceptible to at least one of the three viral antigens; 70 to H1N1, 54 to H3N2 and 32 to the B virus. One hundred and three of these volunteers were actually randomized to be immunized and 92 of them remained in the trial and were challenged with either the H1N1, H3N2 or B viruses.

As I mentioned the primary end point was protection against laboratory documented illness. Forty-five percent of placebo recipients developed laboratory documented influenza illness; 7 percent of the FluMist™ recipients and 13 percent of the inactivative vaccine recipients developed laboratory documented illness. This was consistent with an 85 percent efficacy for FluMist™ and a 71 percent efficacy for the inactivated vaccine. These levels of efficacy were not different between the two vaccines.

In addition to collecting data on the primary end point, the investigators also collected data on the immunogenicity of the vaccines as well as strain-specific efficacy. I've summarized on this slide data for both for you. As you can see, immunogenicity as defined by evidence of a four-fold serum antibody response, was modest in the FluMist™ group, with 10 percent of participants mounting a four-fold antibody rise to the B strain, 29 percent to

the H1N1, 39 percent to the H3N2.

In contrast, the serum antibody response to the inactivated vaccine was demonstrated by more than 90 percent of the participants in each group. Despite the relatively modest serum antibody response, efficacy as defined by protection against clinical illness, was very high in the FluMist™ group as well, as in the activated vaccine group, and therefore, there was very little correlation for recipients of the FluMist™ vaccine between the serum antibody response and efficacy, again, with very high levels of efficacy being observed despite the low serum antibody response in each of the strains.

Next slide. In conclusion, therefore, from the challenge trial, AV003, FluMist™ was highly efficacious providing 85 percent protection and prevention against laboratory documented illness in healthy adults when they were challenged with the wild-type viral strains and this efficacy was observed despite the low serum antibody response.

I'd now like to move on to the large clinical effectiveness field trial. This was a multi-site trial conducted in 13 centers across the United States during the 1997/'98 season. This was also a randomized double-blind placebo controlled trial.

Participants were between the ages of 18 and 64 years and all of them were working at least 30 hours per week. As has already been mentioned, over 4,000 people were randomized in this trial. The randomization scheme was 2 to 1 with twice as many participants receiving live attenuated vaccine as placebo.

I will note that during the 1997/'98 season the predominant circulating virus, the H3N2 A/Sydney virus was poorly matched to the vaccine strain A/Wuhan that was included for that year. This was a single dose regiment as would be the case for adults and we defined the outcome period according to community and national surveillance data that were available. We looked at a variety of effectiveness outcomes in order to achieve a fairly broad assessment of the impact of influenza and its prevention in this population. We looked at the proportion of people with influenza like illness, numbers of illnesses, days of illness, work loss and health care use.

We ascertained outcomes through the use of symptom cards that were completed on a daily basis for each month, November through March of the study year. Participants received twice monthly telephone reminders to encourage them to complete and return the

cards. As mentioned previously, the outcome periods were based on local and national influenza surveillance data. We looked at both site-specific peak outbreak periods because these were expected to provide the most specific or precise estimates of vaccine effectiveness. We also looked at a pooled 14-week total outbreak period.

The site-specific periods were defined based on a pre-specified computer algorithm centered on the modal week for the local geographic area designed to capture at least 80 percent of influenza activity for that season. The total operating period is defined by an expert panel. As has been mentioned previously, for the study participants in this trial, baseline characteristics were well-balanced between the two groups.

In this slide I have summarized for you the influenza surveillance data both for the study sites pool in the red line as well as national data for the season in the vertical bars. As you can see, the experience in the study sites closely mirrored that of the United States for that season. The median duration of the peak outbreak periods was seven weeks. Symptom completion card rates were excellent in this trial. As you can see, they were similar between the

vaccine and placebo groups across the five months of the outcome data gathering period. Ninety-seven percent of participants returned at least one of the five symptom cards and 88 percent returned four or more.

The illness definitions presented something of a challenge for us in this trial. There is no or historically has been no gold standard for the definition of clinical influenza-like illness. Accordingly we considered trade-offs between sensitivity and specificity as we considered illness definitions. A sensitive illness definition was expected to provide us with the most comprehensive assessment of the impact of influenza benefits of vaccination in the population which was particularly relevant from a health economic point of view.

On the other hand, a more specific illness definition would be expected to provide perhaps a more accurate estimate of whether or not the vaccine actually works, that is, is it efficacious. For the primary outcome illness definition we selected the most sensitive and least specific outcome illness, that is any febrile illness with a definition listed here, a febrile illness of at least two day's duration with at least two symptoms as listed over here.

The more specific illness definitions that we included in our pre-specified data planning included severe febrile illness that is a febrile illness lasting at least three days with symptoms on all three days as well febrile upper respiratory illness, that is febrile illness of at least two day's duration but with the requirement that participants actually have respiratory symptoms during the illness. I would say that this illness definition, febrile upper respiratory illness, most closely mirrors the CDC's surveillance definition for influenza-like illness as can be seen here.

And this slide and then the next few slides, I will be summarizing some of the clinical effectiveness results of this trial for the peak outbreak period. Here we have shown the proportion of participants experiencing any illness during the peak outbreak period for the primary end point any febrile illness as well as for severe febrile illness, febrile respiratory illness. We have also included for your information, information on outcomes using the CDC surveillance definition for ILI. As can be seen, there was a reduction in illness events across all the definitions.

However, for the primary end point the

reduction did not reach statistical significance. Not unexpectedly, as we look at the more specific illness definitions, the reduction was larger and we appeared to achieve somewhat more precision in the estimate. Well, in addition to looking at the proportion of participants experiencing an outcome, we also tried to -- we also measured the outcomes looking at event rates. Why did we do that? Because some participants had more than one event and when we looked just a proportions, we actually failed to look at all of the information that was available.

For example, if someone had two or three febrile illnesses and with vaccination would have had only one illness, we would have picked that up when looking at event rates, but not when looking a proportions. When looking at event rates, that is the number of illness episodes, one sees somewhat similar kinds of reductions across all of the illness definitions; again, any febrile illness, severe febrile, febrile upper respiratory illness and the CDC surveillance definition. However, again, the estimates appear to have achieved somewhat greater precision.

We also looked at numbers of days of illness as another parameter, measuring burden of

disease. And in each case, there were substantial reductions in the numbers of days of illness. I mentioned that this was a clinical effectiveness trial. We were interested in a very broad assessment on the impact of vaccination or the prevention of influenza, not only on illness but also on other healthy economic parameters including missed work, health care use and I have summarized the data here for any febrile illness. You can see the reductions we've observed. And likewise, reductions with febrile upper respiratory illness somewhat more impressive reductions with more precision and also with CDC's surveillance definition for influenza-like illness.

In conclusion, FluMist™ was shown to be highly effective in reducing illness, missed work and health care use and this effectiveness was observed during a year when the predominant circulating virus strain was poorly matched to the vaccine. Thank you.

CHAIRMAN DAUM: Thank you, Dr. Nichol. We'd now like to take the two presentations together that dealt with adult issues and have some committee discussion about them. Dr. Katz and then Dr. Schild.

DR. KATZ: Kristin, I wondered in the first study, the challenge study with the rather modest antibody increase but the very significant

protection against illness with challenge. Do you attribute that to local nasal antibody? Did anyone measure that or to cell-mediated immunity? What do you look to as the mechanism there?

DR. NICHOL: Local antibody responses in nasal wash were also assayed in the trial. And in both groups of vaccine recipients, there was some evidence of antibody response that was higher than in placebo. There was no significant difference between inactivated vaccine and the live attenuated vaccine. I think it's the million dollar question, how do we identify the immune correlates with protection. Clearly serum antibody response is not sufficient to explain the immune response that people obviously are having.

DR. KATZ: My second question, it can go to Harry or Paul or anyone which is obviously, you've excluded the major group for whom influenza vaccine is recommended, people over 65 years of age. Is this because you anticipate the vaccine isn't as effective or your -- what was your reason for using 64 years as your cut-off?

DR. MENDELMAN: Mostly Dr. Katz, it's an IRB issue. You're doing an efficacy trial, you can't give placebo to people where the vaccine that's

currently licensed is indicated. And you can do large safety trials comparative to the inactivated vaccine but it won't provide the end point that you need for registration.

DR. KATZ: Thank you.

CHAIRMAN DAUM: Dr. Schild, please. Dr. Schild, could you press that button for us?

DR. SCHILD: Mine is a similar point to Dr. Katz; you're getting better protection in your challenge study with a live vaccine than with an inactivated vaccine and yet you have much lower antibody responses. Therefore HAI antibody is not a very good indicator of protection and whether you attempt to do further studies to really try to find surrogate markers for protection in the live vaccine situation, for example, neutralizing antibody.

DR. ARCURI: We did perform nasal wash IgA antibodies on that test and I won't bother to call up the slide but I could if you want to look at it, but it's a negative result in that there was no difference between placebo and FluMist™ recipients or between ITV and placebo in nasal wash IgA titers. Now, remember, this is a small study so we don't have large numbers.

DR. SCHILD: Oh, yes.

DR. ARCURI: One could spend several days on immunity of influenza after TIV and live virus and I think work needs to be ongoing on markers of protection, but it's been a gnarly problem for a long time.

DR. SCHILD: Thank you.

DR. NICHOL: Might I also just follow up? I showed plate estimates there but if you'll recall confidence interval around the estimates of efficacy actually the live attenuated and inactivated vaccines, we cannot distinguish between those levels of efficacy.

DR. SCHILD: They were small numbers, yes.

DR. NICHOL: So that we would say they were equivalent in this trial.

CHAIRMAN DAUM: Dr. Steinhoff, please.

DR. STEINHOFF: This is a question about the challenge model in the adults. I'm just wondering how you would reflect on the issue that in the placebo recipients. 45 percent of the subjects developed your end point that you were measuring. Do you think that if you had a different kind of a challenge with a higher illness rate among the placebo recipients, you'd find a different protective response? You may not be able to answer that, but the -- how would you

reflect on that question?

DR. NICHOL: You know, I suspect that if there had been a higher illness rate among the placebo recipients, that we might have seen a higher level of efficacy, but, you know, it's my understanding in challenge trials and this was a study conducted by John Treanor and colleagues, that illness rates of 50 to 60 or 70 percent are not uncommonly seen. We saw an illness rate of 45 percent, so whether or not that was much different from what one might expect in other challenge trials, perhaps others would like to comment.

CHAIRMAN DAUM: Dr. Goldberg, then Dr. Stephens.

DR. GOLDBERG: On the challenge trial, if I understand it correctly from your slides --

CHAIRMAN DAUM: Could you speak directly into the mike, Dr. Goldberg?

DR. GOLDBERG: If I understand your slides correctly, it looks like you stratified in the randomization by the susceptible strain. When I add back up the numbers, you've lost the most -- you've got 29 subjects who actually did the challenge in the FluMist™ group, 10, 9 and 10, out of the 36, so that's the group where you lost more subjects for the

challenged. Can you explain that? You randomized 33, 36 and 34 and you had 32, 29, 31 who actually -- you reporting challenge data on. Could someone address that?

DR. MENDELMAN: As an aside, it just showed up. It's really the susceptible B's that drove the sample size because they're multiple -- the adults, you know, are susceptible to, you know, more than one strain, and then at the time of the randomization and the challenge, it was also based on how many people could be housed after the challenge. There were logistical, practical issues.

DR. GOLDBERG: I just wanted to -- my question really addresses the fact that it looks a little differential with regard to not being challenged by strain and I wondered if that meant anything here. There's a differential in the challenge group. Do you want to address that?

DR. MENDELMAN: I'm not hearing the question or understanding it. Sorry.

DR. GOLDBERG: You have 36 subjects in the FluMist™ group, but when you do the challenge, you have 29, so you've lost 7 subjects in --

DR. MENDELMAN: Right, right, there was --

DR. GOLDBERG: -- and that's more proportionately than in the other groups. Is there anything that went on there? Is there any reason for that or is it related to the susceptibility or the FluMist™ itself?

DR. MENDELMAN: No, the reason was practical in how many people could be challenged and housed for the next seven days.

DR. GOLDBERG: It was supposedly blinded, I would think. So did they drop out because they didn't want to be on -- you know, because -- was here anything that went on that might make you -- I mean, I don't know if this would effect the result or not, but I think it is a differential.

CHAIRMAN DAUM: Did someone on the sponsor group want to make a comment because you can't make it from your seat?

DR. ARCURI: The people -- the randomization occurred, a subset were challenged, but the randomization occurred -- was blinded.

DR. GOLDBERG: No, I would expect that. I mean, the only question is, is there something associated with the FluMist™ group that led them not to be challenged? That's really the essence of my --

DR. MENDELMAN: There has not been any,

Dr. Goldberg. We could, if it's okay, Dr. Daum, ask Dr. Wittes to comment, who was involved in the analysis.

CHAIRMAN DAUM: Who is Dr. Wittes?

DR. MENDELMAN: Dr. Wittes is a consultant and she is the --

CHAIRMAN DAUM: Sure.

DR. MENDELMAN: -- head of Statistics Collaborative.

DR. WITTES: But she doesn't talk very well. Obviously, Judy, we looked at that, I mean, because you wonder when you see something. There was nothing that we could see. It was a small group, so -- okay.

CHAIRMAN DAUM: Poor Dr. Wittes. Dr. Goldberg, I think we're done with this issue. We're not going to get any further with it, I guarantee you. Dr. Stephens, Ms. Fisher and someone here, Dr. Steinhoff, thank you, and then Dr. Schild.

DR. STEPHENS: The efficacy data you presented, studies, the healthy adult study was effective -- pretty impressive for the H3N2 virus and the challenge study looked like there was protection, albeit without antibody for the H1N1. Do you have any other data on H1N1, which I think is at least a

concern that I have that you're going to share with us? Maybe you're going to share it later.

DR. MENDELMAN: George, could you call up slide number 10 and 11 under backup's to Dr. Belshe's presentation? So these are the historical data for trials primarily conducted by National Institute of Health and if we could -- can we focus this, George? You can see the range of efficacy, depending on here's H1N1, 79 percent, 29 percent, H1N1, 100 percent, 67 percent, H1N1, 188, H3N2, 172, H3N2, 100/100, H3 -- B's those are all 100. So high efficacy, albeit, these are small trials and challenges, high efficacy overall against the challenge.

The next slide should be the field trials, whether it's H1 or H3, including Dr. Edwards' trial at Vanderbilt, and the efficacies range from 36 percent to it's hard to see, 76 percent.

CHAIRMAN DAUM: Imagine how we feel.

DR. STEPHENS: I'm sorry, just to clarify, I'm asking about FluMist™ specifically.

DR. MENDELMAN: Well, these are the same Master Donor Viruses, that's either a monovalent or a bivalent, that were derived by Dr. Maassab. They're not Aviron trials. They were conducted prior to Aviron, prior to the current trivalent formulation

that we are proposing for licensure.

CHAIRMAN DAUM: Thank you. Ms. Fisher, then Dr. Steinhoff and Schild.

MS. FISHER: Okay, I just want to make sure I understand. With FluMist™ you get a between 10 percent and approximately 25 percent reduction in any febrile illness, severe febrile illness, febrile upper respiratory illness and days of missed work between 10 and 25 percent on average. It's different for different categories. Were you, perhaps, expecting a larger reduction? I mean, is that a healthy reduction in terms of placebo and --

DR. NICHOL: It's not a paltry reduction. It's absolutely what one would expect understanding that even with our more specific illness definitions, not all of the outcomes were influenza related and so to see a 25 percent reduction in febrile respiratory illness, for example, might correlate with if one had laboratory confirmation of only those illnesses that are influenza related, might correlate with an 85 or 90 percent reduction in the influenza related illness.

I have a slide here. I've been, over about 5 or 6 years experimenting with ways to address that point specifically, the difference between efficacy and clinical effectiveness. These are data

not from the AV009 trial because we didn't have laboratory confirmation of influenza documented illness, but these are data that I have adapted actually from the CDC trial conducted over two seasons in Michigan and from the second year of the trial, they looked at influenza-like illness and had laboratory confirmation for approximately 35 to 40 percent of the people who had influenza like illness so only about 30 percent of the influenza like illnesses were actually influenza if you add laboratory confirmation.

If you looked at the difference between placebo and vaccine, you saw a 34 percent reduction in all influenza-like illness but if you looked at the subset of laboratory confirmed, you saw an efficacy of 89 percent. Does that help? So when we see a 25 percent reduction in febrile upper respiratory illness or whatever the numbers exactly are, that perfectly well correlates with some level of efficacy that's the underlying efficacy is much higher.

MS. FISHER: So we really don't know in these cases how many of them were actually influenza.

DR. NICHOL: That's right, they were only clinically defined. We did not have laboratory confirmation. This was a clinical effectiveness

trial. In the challenge trial, we had laboratory confirmation. They were very different kinds of trials, different outcomes and in many ways, different purposes. What the physician sees in the office is influenza-like illness. They see this and when I immunize my population of patients, what I see is in this case, a 34 percent reduction.

If I'd only teased out influenza illness by laboratory confirmation, I would have been able to say that there was an 89 percent reduction in this case, using this example in what was only influenza related. Yeah, it's the difference between influenza attributable or caused specific versus all cause outcomes.

CHAIRMAN DAUM: Thank you very much. Dr. Steinhoff, then Dr. Schild, then I think Dr. Faggett and then we'll go back and finish the sponsor's presentation.

DR. STEINHOFF: This is another question for Kristin on the challenge study. We already talked about the laboratory documented illness rates and they were similar between the two vaccine groups. Could you tell us the infection rates in the subjects in that study?

DR. NICHOL: Yes, I believe that I have

those numbers immediately here for you. I do not believe that I have a slide for you but let me read you the wild-type infection rates by strain and vaccine. For placebo, the wild-type infection rates were 58 percent for H1N1, 50 percent for H3N2, 55 percent for B. For the live attenuated vaccine, they were respectively 30 percent, 44 percent, 20 percent. For inactivated vaccine, they were respectively H1N1, 20 percent, H3N2, 30 percent and B zero percent.

CHAIRMAN DAUM: Thank you very much. Dr. Schild, then Dr. Faggett.

DR. SCHILD: It's really a technical question. It's been shown that on occasion when you isolate influenza viruses from the human specimen from the throat in eggs, you select variants that are antigenically somewhat different from the actual human virus in the throat. This has been shown in several laboratories. The question I have in relationship to the challenge studies is whether the virus you used in challenge was actually cultivated in eggs, and just to comment it might not effect the issue very much but it has been shown in laboratory studies that it can make a significant difference in terms of protection of immunized animals whether the viruses you're using compared in eggs mammalian cells or whether the virus

is directly from human specimens from the throat.

DR. GREENBERG: All the challenge studies that you see -- that you were just presented and that you will be presented the challenge pools were grown in eggs and I think in the historical record that we eluded to previously, that is also the case.

CHAIRMAN DAUM: For the last word of this session, we'll go to Dr. Faggett, please.

DR. FAGGETT: Just a quick question; it would appear that there's quite a bit of allergic rhinitis present in this population manifest post-FluMist™. Do you have any feel for what the pre-FluMist™ incidents of allergic rhinitis was and would this have any impact in terms of antibody response because of the condition of nasal mucosa?

DR. GREENBERG: Dr. Faggett, could you just restate that question.

DR. FAGGETT: Well, you know, you talk about a lot of runny noses but that's usually just either perennially or allergic rhinitis but it could have some impact in terms of --

DR. GREENBERG: You're talking about in Dr. Mendelman's safety study.

DR. FAGGETT: Right, right.

DR. GREENBERG: Can we pull up the slide

of --

DR. MENDELMAN: Is it no a particular slide or is it a different question?

DR. FAGGETT: There was a 20 percent incidents of -- you say runny nose but I'm just trying to get a feel for what the population was -- looked like.

DR. MENDELMAN: This is in children or adults?

DR. FAGGETT: That was adults.

DR. MENDELMAN: That's an 18 percent difference between FluMist™ and placebo recipients, within the seven days, any time within the seven days. We've also done a by day analysis and that's in the slides as well as number of days. Most -- well, more placebo recipients than FluMist™ recipients have no days of runny nose and then there's a distribution on one of those slides that shows that.

CHAIRMAN DAUM: Thank you very much.

DR. FAGGETT: That's all, thanks.

CHAIRMAN DAUM: I'd like to move on now to the last leg of the sponsor's presentation, Dr. Belshe, with a few parting remarks from Dr. Greenberg.

While you're setting up, could I ask folks who want to take photographs of the proceedings to

please not use their flash. It's really somewhat disruptive to the overall proceedings. Photographs are okay, flash is not. Thank you very much.

DR. BELSHE: Thank you very much. I'm delighted to have an opportunity to present the effectiveness and efficacy field trial that was jointed conducted by the NIAID and Aviron in children. I'm going to summarize the study in four parts. This was a two-year efficacy field trial. I'm going to first describe the results of year 1 in which both Influenza A and Influenza B circulated and those strains were well matched to the strains contained in the vaccine.

Then I'll turn and talk about efficacy in year 2 which was an H3N2 outbreak. This was the first year that Influenza A/Sydney appeared and the vaccine was not well-matched to the epidemic strain. Then I'll turn and talk about the analysis of combined efficacy for both years and then summarize the challenge trial we did with H1N1 vaccine strain to obtain surrogate data on efficacy against this virus.

This clinical trial was governed by a steering committee that consisted of the principal investigators shown here on this slide. Many of them are here in the audience today. The steering

committee also consisted of representatives from the two sponsors, NIAID and Aviron and we had the benefit of biostatistical expertise from actually four sources. Both sponsors and then contractors to both sponsors provided substantial input into the design conduct and analysis of the trial.

Now, this figure summarizes the design of the study. This was a double blind, placebo controlled study, randomized 2 to 1, FluMist™ to placebo. Healthy children were enrolled at age 15 to 71 months. The regiment consisted primarily of two doses of vaccine in year 1. At two centers, however, by design only one dose of vaccine or placebo was given and that gave us an opportunity to assess one-dose efficacy as well.

In year 2, subjects where not re-randomized. They remained blinded and were revaccinated according to the initial randomization with either the vaccine or placebo with a single dose revaccination. The primary end point of this study was protection against culture confirmed influenza among the children who had received two doses of vaccine.

Now, we performed active surveillance during the post-vaccination period for adverse events.

All parents were called on day 4 and again on day 10 after each dose of vaccine and then between the vaccination doses, parents were called at two to three weekly intervals to inquire about the health of the child. And before -- after dose 2 and before influenza season began, parents received additional calls at 2 to 3-week intervals to determine safety information.

Now, once influenza season began, which in year 1 was mid-November, we called the families approximately every week, to remind them to report any evidence of influenza and based on what we heard over the phone, we would decide then whether or not to visit the children and culture them for influenza. And we set our sensitivity extremely sensitive, that is a runny nose and a cough was sufficient to trigger a culture for viruses.

Enrollment into the trial is summarized on this slid for year 1. One thousand and seventy children were randomized to receive FluMist™ and 532 were randomized to receive placebo. Most of the children were randomized to receive two doses of FluMist™ or two doses of placebo. Now, the occurrence of influenza in the total study population, that is both placebo subjects and vaccination

subjects, is summarized in this figure. In year 1 we had initially a H3N2 outbreak that was influenza A/Wuhan like and this was followed very shortly by an influenza B outbreak, that was influenza B/Harbin-like and this was similar to what was in the vaccine. And I'll turn and talk about year 2 in a minute.

Now, when we analyze the occurrence of influenza according to a study group, there were only 14 cases of culture confirmed influenza in the FluMist™ group for an attack rate of just over one percent. Seven of those were influenza A and seven of those were influenza B cases. However, among the 532 placebo subjects, there were 63 children with culture confirmed influenza A for an attack rate of almost 12 percent, 37 children had influenza B for an attack rate of 7 percent. Now, that's 100 cases.

Those 100 cases occurred in 94 children because 6 of the children had two illnesses one with influenza A and another with influenza B. Overall the attack rate in year 1 in the placebo group was 17.7 percent. Now, when we do the efficacy calculation against the primary end point, that is children who received 2 doses of vaccine, we get a point estimate of 93 percent efficacy against culture confirmed flu with relatively -- a very narrow confidence intervals.

One dose was also effective. It was almost 89 percent protective against culture confirmed flu and an intent to treat analysis revealed 92.6 percent efficacy against influenza.

Vaccine was also protective against significant clinical illnesses associated with influenza and this particular analysis looks at febrile illnesses and otitis media. For culture confirmed febrile illness, there were only eight cases among the 1,070 FluMist™ recipients. In contrast there were 80 cases among the 532 placebo subjects for 95 percent efficacy against febrile influenza.

Now otitis media is a common complication of influenza and we observed 20 cases of otitis media among those children in the placebo group who had culture confirmed flu and only one case of otitis media in the children in the vaccined group with culture confirmed flu and so that's 97-1/2 percent efficacy against influenza associated otitis media.

Now, in addition, among the FluMist™ recipients who developed breakthrough influenza, the disease appeared to be more mild at least as indicated by duration of fever. As shown here in the footnote, FluMist™ recipients who had flu, had an average or 2.4 days of fever. In contrast, placebo recipients

who had fever -- who had flu had 4.1 days of fever.

Now, in year 2, 85 percent of the children re-enrolled in the study, 917 were in the FluMist™ group and 441 were in the placebo group and they received a single re-immunization according to their original randomization. Influenza A occurred in year 2. It was the first year that influenza A/Sydney occurred, it's shown here in the red line and there was a single case of influenza B. Now, when we look at the breakdown of those cases according to the treatment group, there were 15 cases among the 917 placebo recipients but 56 cases among the 441 placebo recipients.

Now, the outbreak of influenza A that year was primarily influenza A/Sydney but there was some influenza A/Wuhan or vaccine-like viruses circulating in the community. So we strain typed each of those viruses and this particular slide illustrates the efficacy according to the strain specificity. So the vaccine contained A/Wuhan and then we had wild-type A/Wuhan occurring in a few of the patients. There were four such cases and then there was a single B/Harbin occurring. So I've lumped together in this analysis the vaccine-like viruses and vaccine then was 100 percent effective because these five occurred all

within the placebo group and there were none in the vaccine group.

Most of the viruses were A/Sydney-like, 15 of those occurred in the FluMist™ group and 51 occurred in the placebo group which gives us a point estimate of about 86 percent efficacy. Overall, for all cases of flu in year 2, vaccine was 87 percent protective. Now, in order to understand this high efficacy of the live attenuated vaccine against a significantly drifted virus, a subset of children who were initially seronegative and received two doses of vaccine in year 1, were analyzed for HAI antibody against the vaccine strain shown here in the first column, which is the percent of children with four-fold rise, and a variety of related H3N2 viruses using antigens provided by the FDA.

And so this is the proportion of children with four-fold antibody rise to vaccine and the next column is influenza A/Sydney and then the other viruses here are A/Thessalonika '95, Russia '95 and Johannesburg '94. And so there appeared to be a very broad reacting antibodies directed against H3N2 viruses after vaccination with FluMist™.

We also had an opportunity to look at protective effect of natural infection in year 1 with

A/Wuhan upon the A/Sydney outbreak in placebo children. So what I've got here is the 441 placebo recipients broken down by group according to whether or not they had culture confirmed influenza A/Wuhan in year 1. And there were 52 placebo subjects in whom we had isolate A/Wuhan in year 1 and only one of those had A/Sydney in year 2.

In contrast, there were 389 placebo children without culture confirmed H3N2 in year 1 and we had 54 had culture confirmed influenza A/Sydney H3N2 in the second year. And so this gives us an efficacy rate then of 86 percent which is the same point estimate we get for vaccine. So to turn that around a little bit, it appears that live attenuated vaccine was just as effective as a recent natural infection with a related but significantly drifted H3N2 virus.

In year 2 we also observed significant benefit against clinical disease associated with culture confirmed influenza. This is the same analysis for year 2 as I showed you earlier for year 1. Febrile illness associated with culture confirmed flu, there were only 12 cases in the 927 FluMist™ recipients, but there were 54 cases among the 441 placebo recipients. That's an efficacy of 89 percent

against febrile influenza and similar to year 1, there were a lot of case of otitis media associated with influenza. In the placebo group there were 17 case, in contrast there were only two cases of influenza associated otitis in the FluMist™ group which is 94 percent protective.

And finally we also observed in year 2 FluMist™ was protective, seemed to reduce the severity of illness against A/Sydney. The duration of fever in the breakthrough cases in the FluMist™ group was only 2.1 days in year 2. In contrast, the duration of fever in the placebo recipients was 4.9 days and that was a significant difference.

Now, to do an analysis of 2-year efficacy we did a Kaplan-Meier analysis and the display of this data is shown as acquisition of influenza in the placebo group shown in the top part here with 95 percent confidence intervals versus the vaccine group and this is over the time in the study. So that initially children start out, they've not had flu and they're being vaccinated and then at this point, we had the H3N2 outbreak in year 1 and these curves very quickly diverge as placebo children acquired H3N2.

And at this point, the slope changes and this is the influenza B outbreak in year 1 as children

acquire influenza B. And then we get to the intervening summer months when there is no flu and children are revaccinated in the fall and then at this point, there's the outbreak of influenza A, H3N2 Sydney and at the end of two years, a third of the children in the placebo group have had culture confirmed flu. In contrast, only about 2-1/2 percent of vaccinated children had culture confirmed flu. And there's a 92 percent reduction then from this point to this point and the 2-year protection against influenza.

Vaccine was also protective against lower respiratory disease associated with influenza. And this analysis looks at year 1, year 2, and the 2 years combined. In year 1 there were four cases of lower respiratory disease, 3 of them occurred associated with culture confirmed flu. Three of them occurred in the placebo group, only 1 in the FluMist™ group, that's 83 percent efficacy but the confidence interval includes zero. However, in year 2, influenza A/Sydney was a particular virulent virus. There were eight cases of lower respiratory disease, all of them in the placebo group or 100 percent efficacy. Lower bound on the confidence level is 77 percent.

Overall in the two years of study there

was 95 percent protection against lower respiratory illness associated with influenza. Now, this is a similar display as we just discussed for adults which illustrates the difference in efficacy and what we mean by effectiveness. And in this particular data I'm showing you is the -- represents -- the height of the bar represents the attack rate of all febrile illness that we observed in the 2 years of study in this clinical trial, and the left-hand bar is the placebo group, and the right-hand bar is the vaccine group.

Now so far we've been talking about efficacy which looks then only at the laboratory documented influenza which is a portion of this bar because clearly there are many other causes of fever and we don't expect the vaccine to have efficacy against other causes of fever and so what we've been looking at is, is this portion of the bar versus this portion of the bar in vaccinated subjects and we get efficacy of 94 percent against febrile influenza.

If we now turn and look at what's the benefit of the vaccine on the overall health of the child, we then say, okay, let's look at the total height of the bar in the placebo group versus the total height of the bar in the vaccine group and we

get effectiveness of 18 percent. So we can expect vaccine to reduce all febrile illness but about 18 percent. So with that as an introduction, let's look at several other effectiveness measures from this trial and I'm showing you the overall 2-year effectiveness.

The vaccine reduced febrile illness associated with antibiotics by 23 percent and that was statistically significant. Vaccine reduced febrile otitis media with antibiotics by 30 percent and that was statistically significant. Vaccine reduced the days that children missed daycare by 12 percent and similarly parents didn't have to lose as much work by 12 percent. Those two measures did not quite achieve statistical significance.

However, there was a significant reduction in the number of health care provider visits in the vaccine group. There was an overall 11 percent reduction in visits to the doctor. So by a number of measures, FluMist™ improved the health and well-being of children. Now during the two years of this field trial, H1N1 viruses did not circulate and therefore, the steering committee got together and designed a follow-on study where a subset of children were asked to be challenged with H1N1 vaccine strain. The

challenge was a high dose 10^7 given by the spray device and children were challenged 5 to 8 months following the second year of study.

One hundred forty-four children had received prior FluMist™ and 78 children had received prior placebo. The primary end point of this study was protection against viral shedding H1N1 vaccine virus. Now, before we did this challenge, we obtained serum for HAI antibody and nasal washes for IgA so that we could determine correlates of protection and we assessed a viral shedding on days 1 through 4.

A summary of the viral shedding is illustrated here. Of 142 prior FluMist™ recipients who had viral shedding tested, only 6 shed virus. In contrast, of 77 tested placebo recipients, 19 shed vaccine virus on days 1 through -- on any day 1 through 4 which gives an efficacy, a point estimate of efficacy of about 83 percent. The analysis of the correlates of protection is long and complex and I'd be happy to discuss that with you, but just to summarize those results here, we demonstrated that overall any serum HAI antibody was associated with a 93 percent reduction in the attack rate of viral shedding. Any nasal wash IgA antibody was associated with an 85 percent reduction in attack rate of viral

shedding. In addition to that, there were a subset of children in the FluMist™ group who had neither HAI antibody nor nasal wash IgA and simply having a history of receiving vaccine correlated with protection against viral shedding.

So we conclude then, that FluMist™ provided a very high degree of protection against culture confirmed influenza during two seasons of this efficacy field trial. FluMist™ provided a high degree of protection in year 2 against a significantly drifted H3N2 virus and FluMist™ protected against significant influenza associated clinical illnesses, including otitis media febrile illness and lower respiratory infection. Thank you.

CHAIRMAN DAUM: Bob, thank you very much for a very clear presentation. I think what I'd like to do is, Dr. Greenberg, it looks like your final comments will be quite brief.

DR. GREENBERG: Mercifully.

CHAIRMAN DAUM: Mercifully, no, that's your word. And so could we hear them and then have a few minutes of committee discussion. We will then take a short break and then have the FDA presentation.

DR. GREENBERG: Just out of curiosity, where are we with our 90 minutes?

CHAIRMAN DAUM: You are at 91 minutes, so you're actually at minus 1 but I presume you're only going to take 2 or 3 and we can tolerate that:

DR. GREENBERG: Thank you. I'd like to thank all of you for being so attentive and I'm not just going to very briefly summarize what you've heard. I think from the data you've just listened to you would agree with me that FluMist™ is safe, well-tolerated, effective and efficacious in healthy children and adults 1 to 64 years of age. The efficacy was shown in four different trials both challenged trials and field trials and I want to remind you that the efficacy we showed is consistent with the efficacy that Dr. Murphy talked about in all the historical record with multiple trials of this vaccine over many years. So the efficacy really is a continuum and we've shown it again.

FluMist™ protected against disease due to antigenically well-matched influenza viruses and against an antigenically drifted strain in both children and adults. And FluMist™ was effective in reducing antibiotic usage, health care provider visits and days of lost work. Next slide, please. Well, so FluMist™ is safe and effective and that's highly important because we're going to prevent a disease

that causes a lot of problems for everybody and I know I'm boring you but that's the mission of this vaccine. FluMist™ will provide an additional vaccine supply in a situation where vaccine is limited and the need is great. It has an ease of administration which you all are aware of and most importantly, I think prevention of influenza -- it will prevent influenza in healthy children and adults and I want to emphasize the children because as we said at the beginning of this presentation, children are really under-served, vis-a-vis, vaccination at the present time. Less than 10 percent of children are vaccinated and there's a tremendous burden of disease on those children and they represent a potential nidus of infection to the rest of the community.

Next slide, please. As you are all aware, the story of this vaccine is a very long one and many, many people have contributed to it and I couldn't put all the names on a single slide. I'd like to simply remind you that Dr. John Maassab, who cannot be here today, was the originator of this vaccine and has really been involved with it over a 30-year period. The National Institute of Health and more specifically the National Institute of Allergy and Infectious Disease and even more specifically, that's

intramural, even more specifically the vaccine treatment evaluation units have played a very big role in the development of this vaccine. Numerous clinical investigators outside of those groups have been involved and finally my colleagues at Wyeth Lederle Vaccines have also helped. Thank you.

CHAIRMAN DAUM: I'd like to thank the sponsor for essentially adhering to our constraints and providing us with a stimulating set of data to consider and I'd like to have some questions on Dr. Belshe and Dr. Greenberg's presentations before break. Dr. Kohl, Dr. Griffin and Dr. Katz.

DR. KOHL: Dr. Belshe, 2 questions. You may not have the numbers because it's a sub-group, but do you have specific protection numbers age 12 to 24 months.

DR. BELSHE: Yes, that is in fact in the FDA briefing booklet.

DR. KOHL: I didn't see it.

DR. GEBER: It's 15 months.

DR. BELSHE: It's months, yes.

DR. KOHL: Okay, 15 to whatever.

CHAIRMAN DAUM: It's just being called up.

DR. KOHL: Okay, and then while we're calling that up, in the children who were challenged

in the H1N1 challenge of the FluMist™ recipients who did not shed the virus, a fairly large number, did they have an antibody response? Did you get sera on them to see if even though they didn't shed, whether you could boost their immune response with a challenge?

DR. BELSHE: We didn't go post-challenge sera in these children. They'd been manipulated a lot in 2 years and in order to be practical and bring this data to an end, we did not do that.

DR. KOHL: It's too bad because the question comes up will the immune response be blunted or whatever by multiple episodes of immunization and that would have been a neat chance to see if they continue not to response.

CHAIRMAN DAUM: Thank you. Dr. Griffin.

DR. GRIFFIN: Since the efficacy was actually pretty similar for whether you got 1 dose or 2 doses, I was wondering what the reasoning is behind recommending 2 doses for the youngest children.

DR. BELSHE: There's a long history of studying multiple doses by the NIAID as well as more recently by Aviron and what we've seen is that H3N2 and B very reliably give a vigorous antibody response it seronegative children and appear to in some -- what

we've called, the investigators have called interference reduce the response anyway to H1N1 with the first dose. And that this is overcome by just repeating the vaccination 30 to 60 days later.

DR. GRIFFIN: Is that unique then to the youngest children?

DR. BELSHE: Well, it's only observed in triply seronegative individuals and that -- it really means young kids.

CHAIRMAN DAUM: Thank you. I think three committee members wanted to ask the same question at once, so we'll go on to Dr. Katz and then Dr. Edwards.

DR. KATZ: With permission, my question is for Nancy Cox. Every year you show us studies at ACID of ferret anti-sera and various cross reactivities. What's the difference in your studies between Wuhan and Sydney? I mean, how far apart are they?

DR. COX: There were very consistent 4-fold to 8-fold differences using post infection ferret sera and there were -- I don't remember if -- they were in both directions but I can't remember if it was greater in one direction than the other, but there was what we would consider to be a significant difference and the vaccine strain was updated in the next year.

DR. KATZ: Thank you.

CHAIRMAN DAUM: Dr. Edwards and Dr. Daum.

DR. EDWARDS: That actually is a nice prelude to my question. Are you suggesting that the cold-adapted vaccine is unique in it's heterotypic protection compared to the inactivated vaccine from your suggestions?

DR. GREENBERG: No.

DR. EDWARDS: Thank you.

CHAIRMAN DAUM: I'm wondering about children or adults for that matter who fail vaccine and I know that certainly in other settings particularly bacterial infections when you have a child that fails a vaccine during a trial where you sort of run around and study every possible thing about that person. What do we know about the people who fail trials, trials like we've heard today? Have we made any attempt to look and see if there's anything special with their exposure, their clinical situation, their immunity, their ability to be a good host?

DR. BELSHE: Well, the problem, of course, with studying a vaccine that has 94 percent efficacy is that you get very few failures and so we just do not have the pre-immunization and post immunization immunologic assessments on enough children to make any

comments about why is it that small subset fails.

CHAIRMAN DAUM: Ms. Fisher and then I think we'll break.

MS. FISHER: So if HAI -- serum HAI antibody is not a correlate for immunity then the only way to measure it is through challenge? In other words, you measure efficacy by direct challenge.

DR. BELSHE: No, serum HAI antibody is clearly a correlative protection but it's not the only correlative protection. IgA antibody in the nose is also an important correlative protection. So we clearly have shown that in children. We have two good correlative protection but there is something beyond that. There is something beyond that because a subset of children without HAI antibody and without IgA antibody are still protected.

MS. FISHER: So you just don't know the mechanism.

DR. BELSHE: That's correct, not in that subset.

CHAIRMAN DAUM: Okay. Again, we thank the sponsor for a great deal of data and food for thought so to speak. It's now 4:00 o'clock. We will begin the FDA presentation promptly at 4:15.

(A brief recess was taken.)

CHAIRMAN DAUM: We'll now continue, please, if everyone will take their seats. We'll turn the floor over to Dr. Mink, ChrisAnna Mink, from the FDA to initiate the FDA presentation.

DR. MINK: Can you hear me okay? I will present the clinical summary from FDA on the Aviron cold-adapted, live attenuated influenza virus vaccine FluMist™. Let me re-emphasize what Dr. Levandowski stated this morning that this BLA was submitted on October 31st, 2000. Our review is ongoing and many of the data have not been submitted or have not yet been submitted in final format. I also need to give my eternal gratefulness to my clinical review team, and my supervisor, Dr. Geber and our statistician, Dr. Wasima Rida. I hear an echo, do you?

CHAIRMAN DAUM: There is an echo in this room. The sound bounces around and comes back. I don't know what to do about it.

DR. MINK: That's okay, just so it's inside my head.

CHAIRMAN DAUM: Can people in the back -- we can't rule that out unfortunately. We can rule that out. Would everybody please turn their cell phones and beepers off. If anyone needs any help, as someone told me this morning, shutting it off, let me

know. Dr. Mink.

DR. MINK: The indication sought is active immunization for the prevention of influenza in children, adolescents and adults from 1 to 64 years of age. Two-dose regiment at least 30 days about is being requested for the first 10 years in 1 to 9-year old subjects, less than 9 years and one-dose regiment for those over 9 years to 64 years of age also for immunization of travelers to areas where influenza viruses are circulating.

In this section, I will discuss studies in support of efficacy. You've heard a little about most of these already, the pediatric efficacy trial, AV006. AV011 is the efficacy against shedding a vaccine strain H1N1 following -- AV009 is efficacy against illness during influenza outbreak periods in adults 18 to 64 and AV003 is efficacy against challenge with wild-type virus. In this section I will also review studies submitted in support of consistency of manufacturing; AV007, which is a lot consistency trial and AV014 which is bridging of FluMist™ blended and filled at 2 different facilities.

To begin, I'll start with AV006. As described to you, this is a U.S. multi-center 2-year trial prospective double blind randomized in 2 to 1

ratio in healthy children 15 to 71 months of age. It was initiated for the 1996/'97 influenza season and evaluated by a 1-dose or a 2-dose regiment which was separated by 60 days. FluMist™ was delivered via AccuSpray™ device of .5 mL dose. The type that's shown here in the year 1 was A/Texas H1N1, year 2 was A/Shenzhen of H1N1 and both years the H3N2 A/Wuhan and the B was Harbin '94-like. As has been said there, the placebo was normal allantoic fluid, which I'll abbreviate as NAF, stabilized with SPG.

Monitoring for efficacy was performed by active surveillance with phone calls every two to three weeks starting on day 11 post-vaccination. Calls were increased to every 7 to 10 days with influenza outbreaks. Parents were to call if their child had any illness consistent with influenza. Pre-defined criteria for obtaining influenza cultures or at the investigator's discretion were reasons for the subjects coming in for cultures. This was after day 11. Per protocol, to minimize risk of unblinding, cultures of subjects was discouraged in the first 10 days post-vaccination.

The end points were -- the first episode of culture confirmed influenza illness any time on the day of or after receipt of the second dose of vaccine

was the primary end point. Secondary end points included first episode of first culture confirmed influenza illness occurring at least 15 days after the first dose of vaccine and the subject after receipt of 1 or 2 doses both those enrolled to receive 2 doses and those enrolled to receive 1 dose.

To briefly review, the enrollment of the subjects for both the 1 and 2-dose regiments were comparable demographics, for mean age, ethnicity, gender and for those subjects about 50 percent of the study group had a primary caretaker who was working outside of the home.

The number of cultures obtained is shown in this slide. There were 139 cultures that were positive for an influenza virus out of the 3,127 cultures obtained. Of the -- 18 cultures were obtained within the first 14 days, which I will discuss in a moment. Seven cultures are not included because they were lost or could not be confirmed or had other procedural problems. Six placebo subjects had cultures positive for H3N2 and then subsequently for Type B. This left a total of 114 influenza positive cultures from 108 subjects that were included in the efficacy analysis.

As has been stated, there was H1N1

circulating in year 1 and thus, I do not have field efficacy data to present for this strain. This is a busy slide that shows the efficacy against culture confirmed influenza illness and so this would be those who received 2 doses and those with 1 dose and then all regimentized participants. These are the number of positive subjects and the estimated efficacy was 95 percent confidence levels. As stated by the sponsor, a high degree of efficacy was noted for those who received 2 doses which shows the --

There was also an efficacy stated for those who received 1 dose but because of the small number confidence levels were wider. And again, for all randomized participants, efficacy was demonstrated. The sponsor also provided efficacy analysis for age, gender and ethnicity. This shows results by age. For those less than 24 months which would be 15 to 24 months, the middle age groups and the highest were those over 60 months to 71 months. As you can see, the numbers are smaller but there's efficacy demonstrated and again some of the confidence levels are wider.

On the next slide, it shows efficacy by gender and ethnicity. There was no difference appreciated against any strain for subjects enrolled

in 2 doses between male and female and between Caucasian and non-Caucasian. As mentioned earlier, culturing in ill subjects was discouraged in the immediate post-vaccination period. However, as shown on this slide, some cultures were obtained. A total of 116 subjects who were ill, had 117 cultures obtained in the first 14 days post-vaccination. Of these 116, 38 were placebo recipients, 16 of those had cultures after day 11 which is per protocol. Twenty-two had cultures between days 2 and 10 and zero of those were positive for an influenza vaccine strain.

Seventy-eight of the subjects were FluMist™ recipients, 66 were cultured after day 11 and 17 were obtained between days 2 and 10 which grew 18 cold-adapted incidents of virus strains. As I mentioned, of these 17 FluMist™ there were 18 cultures, they grew 20 CAIV isolates. There were 11 that grew Type B, five Type A and two that grew A and B. I do not have the growth of other viruses at this time but I'm sure this analysis is available from the sponsor or will be soon.

Of note, 16 of the 17 subjects with positive cultures were from the Houston site. As background for the audience, culturing was performed in a total of 31 out of the 144 of the FluMist™

recipients, which was 21 percent and 18 percent of the placebo recipients at that site had cultures obtained within the first 14 days. The illness profiles of these subjects is shown on this slide. I have presented here the placebos that were culture negative for CAIV, that's 36. There are two that I'm not sure of the culture results, so it's presumably negative for CAIV. Seventeen who were positive for CAIV and there were 60 subjects that were negative. As you can see, any illness event, a reactogenicity event or adverse events was identified in 100 percent of the subjects who were culture positive.

More than three events were identified, which is .6 percent which is compared to 41 percent of the negative subjects for our CAIV strain. Forty-one percent compared to 13 percent of the FluMist™ recipients who grew vaccine virus met criteria for CDO influenza-like illness and finally fever occurred in 70.6 of these positive subjects compared to 23 percent of the negative and 23 percent of the placebo subjects. Thus, this would suggest that children who grew a cold-adapted influenza virus strain were ill.

There is some suggestion that HAI titers greater than 1:32 have been associated with protection after natural influenza and after inactivated vaccine.

In AVO06 a subset of subjects had serum HAI and serum IgG and nasal IgA, anti-HA antibodies measured. I will briefly discuss the HAI results. The pre-vaccine titers are shown for this category and in that protocol seronegative was defined as less than 1^4. For H1N1 the GMT was 5.4. The geometric mean titer for H3N2 was 9.5 and for B it was 4. Post-dose 1 was increased modestly for H1N1 and there was a notable increase for H3N2 and for Type B.

Post-dose 2, H1N1 had a rise to 18.8, H3N2, 43.8 and B to 25.8. Please note that the placebo post-dose 2 were comparable to the pre-vaccine titers of the FluMist™ group. This slide presents similar data but shown as geometric mean fold rise. Post dose 1 to H1N1 was an 8.7 rise and there is at least a 4-fold rise for both H3N2 and B and post-dose 2, an increase of 3.4 from baseline for H1N1 and increase of up to 6.3 GMFR was noted for Type B. There we go. I'm okay, I think I've got it. Thank you very much.

In year 2 approximately 87 percent of the subjects returned for participation. In this protocol the subjects received 1 dose of the same study vaccine that they had received in year 1, that is they were not rerandomized. The primary end point was efficacy

against the first episode of culture confirmed influenza illness caused by a sub-type antigenically similar to the vaccine strain. Antigenically similar was not pre-defined in the protocol. The circulating H3N2 as previously described was A/Sydney as was noted to be a variant from the vaccine strain A/Wuhan. Again there was no H1N1 circulating in year 2.

The efficacy in year 1 as shown on this slide for all year 2 participants against all community acquired strains, the efficacy was approximately 87 percent with rarely -- fairly narrow confidence intervals. For the missed strain the asterisk as A/Wuhan and B the efficacy was 100 percent but there are a few cases and we have wide confidence intervals. And for the variants, the efficacy was 85.9 percent. In the H1N1 challenge study, because there was no field efficacy available for H1N1, a challenge study was performed with the primary objective to compare viral shedding of vaccine strain, cold-adapted influenza monovalent or H1N1, and previous FluMist™ compared to previous placebo recipients.

A subset of AV006 subjects approximately 220 of them, about 20 per site, were challenged with vaccine strain H1N1 and then viral shedding was

assessed as a surrogate for vaccine efficacy. In this study design on day zero the subjects were challenged with .5 10^7 $TCID_{50}$ of the vaccine monovalent A/Shenzhen. This was the same lot as H1N1 as used in the FluMist™ for the 1997/'98 season, the year 2 of AV006. The challenge was performed about 5 to 8 months after the year 2 dose. On days 1 through 4 the subjects had nasopharyngeal cultures obtained.

Efficacy against vaccine shedding is shown on this slide. Shedding on any day, frequency denoted by K, occurred in 4 percent of prior FluMist™ recipients compared to 25 percent of prior placebo recipients for an efficacy of 82.9 percent against shedding of monovalent vaccine H1N1. Percent shedding is shown on this part of the graph and as you can see, on days 2, 3, and 4, there was significantly more shedding noted in the placebo recipient, prior placebo recipients than in the prior FluMist™ recipients.

Please also note that shedding still occurred on day 4 for 8 percent of the subjects in the placebo group. There were no subsequent cultures obtained and the total duration of shedding cannot be determined. For adult experience, an effectiveness trial was performed, AV009, as presented earlier. This study involved healthy working adults from 18 to

64 years of age, randomized 2 to 1 FluMist™ to placebo. The subjects received one dose of the vaccine for 1997/'98 composition of A/Shenzhen for H1N1, A/Wuhan and B/Harbin-like.

In this trial vaccines could be self-administered or delivered by study personnel. The primary objectives were to show safety and tolerability of the FluMist™ and placebo the normal allantoic fluid preparations and to show smaller proportions of FluMist™ recipients had any febrile illness during influenza outbreaks. There were several secondary objectives as described by Dr. Nichol.

The effectiveness results are shown in this slide. Any febrile illness occurred in 13.2 percent of FluMist™ recipients compared to 14.6 percent with a reduction of 9.7 percent, with these CBER-generated confidence intervals provided. The p-value, unadjusted for multiple comparisons was not statistically significant for this primary end point. Effectiveness was demonstrated for severe febrile illness, reduction of 17.4 percent, febrile URI reduction of about 22 percent and for the post-analysis of the CDC influenza-like illness and the Department of Defense influenza-like illness with

these p-values are shown.

The rate of AFI or any febrile illness associated events is shown on this slide and as described earlier, these were the number of days or the number of events per 1,000 subjects, per 7-week outbreak period. There were statistically significant decreases for days of over the counter medication use and days of antibiotic use. But the decreases were not statistically significant for days with health care provider visits and missed work days.

In the next slide I will describe study AV003 which was presented to you earlier. Though this is a small study and was performed early in the clinical development of FluMist™, it provides useful information and that is the only data available in adults with culture results for influenza virus. The goal of this study was to assess the efficacy post-challenge with wild-type influenza against laboratory documented illness is subjects 18 to 42 years of age.

FluMist™ was compared to placebo and FluMist™ was also compared to the trivalent in activated vaccine. The other goal was to assess safety and tolerability of FluMist™ in adults who were serosusceptible to at least one of the strains in the vaccine. Study definitions are reviewed briefly

here and that symptoms of influenza -- for laboratory documented illness, symptoms of influenza with shedding of wild-type influenza on one or more days and/or a greater than or equal to 4-fold rise in HAI antibody titers to the challenge virus from days 28 to 56.

Illness was defined as two consecutive days of at least one respiratory symptom of moderate or greater severity or two symptoms of any severity. The strains used were A/Texas for the H1N1, A/Shendong for H3N2 and B/Panama for the Type B. These were contained in the 1994 strains for FluMist™, also in the licensed TIV produced by Evand Medeva and in the challenge strains which were described by Dr. Greenberg.

Placebo included an intranasal challenge -- I'm sorry, intranasal dose of normal allantoic fluids with SPG as described earlier and the injection with a saline with .01 percent thimerosal. Efficacy against laboratory documented illness, any strain, is shown here. In the FluMist™ subjects this occurred in 7 percent with compared to placebo an efficacy of 85 percent, competence intervals for 28 and 100. For the inactivated licensed vaccine, laboratory documented illness occurred in 13 percent, also

compared to 45 percent in the placebo group with an efficacy of 71 percent. The efficacy estimates for the FluMist™ and the TIV were not statistically different.

Next, I'd like to briefly review the lot consistency trial. This is performed to -- to compare the safety tolerability and immunogenicity of 2 doses given 28 to 60 days part of 3 consistency lots of FluMist™ performed in healthy children 12 to 36 months of age. There were approximately 100 subjects per each study group. And lot consistency was to be declared if they could rule out a greater than 4-fold range in post-dose strain specific HAI geometric mean titers across lots with 95 percent confidence.

This slide shows the ratio of GMTs were all less than the pre-defined criteria of 4-fold, the largest difference being noted for lot 2 to 3 of 2.12 with these confidence intervals. The manufacturing bridging study AVO14 was performed as a prospective randomized 3 to 2 ratio of FluMist™ to placebo. Double blind trials compared the safety and tolerability of vaccine blend and filled at two facilities, Medeva and Aviron-PA. The Medeva facility was used for vaccine production and all of the -- for all of the vaccines in clinical trials.

The two primary -- two co-primary objectives are seroconversion rate in seronegative subjects should differ by no more than 20 percent and that 90 percent confidence intervals for the GMT ratios were within 1/4 and 4. In this study, 2 doses 28 to 40 days apart were given to healthy children, 12 to 42 months of age and this study was performed in Australia, to limit interference by circulated influenza in the Northern Hemisphere.

Post-dose 2, the baseline percents for conversion are shown on this slide. For H3N2 and Type B there was zero percent difference and for the H1N1 there was 16 percent difference.

So in conclusion, for efficacy, efficacy was demonstrated against culture confirmed influenza after 1 or 2 doses in healthy children from 15 to 71 months of age in year 1 and again, after revaccination in year 2. Influenza-like illnesses occurred in children who shed CAIV vaccine strain virus post-vaccination. In adults there was no significant decrease in AFI during influenza outbreak periods. And at this time we have no field efficacy data for H1N1.

Next I'd like to review the safety summary. Safety monitoring categories generally are

shown in this slide included reactogenicity events, REs, which were solicited post-vaccination events generally monitored for 10 days in pediatric trials and seven days in the adult trials. The list of these REs were provided by Dr. Mendelman.

Other adverse events, abbreviated as other AEs, were unsolicited AEs also captured in the post-vaccination period. Serious adverse events were consistently defined in the protocols with the Code of Federal Regulations. Generally, these were captured for 42 days post-vaccination in the studies where they were monitored. Not all studies had active monitoring for all categories of adverse events.

The studies that I will briefly review include the safety data from the efficacy trial AV006 and also in pediatric trial of AV012 mentioned this morning, the herd immunity trial performed primarily in an HMO in Texas and then the Kaiser trial AVO19 where they captured medically attended events and SAEs in children 1 to 17 years of age.

Studies submitted in support of safety in adults included effectiveness trial, AV009. Additional studies which I will not discuss today include Phase 1 and Phase 2 trials as well as the safety in AV003. And then because of the chance of

inadvertent exposure for at-risk subjects, studies for safety profiles in asthmatics, 9 to 17 year old, also asthma subjects in AV012 and then an NIH trial which evaluated the safety profiles of FluMist™ and HIV-infected subjects will briefly be reviewed.

I mentioned earlier that the review is ongoing. The sponsor has presented larger numbers for total exposure than we have completed review in the FDA data base. And our data base as of April 30th, 2001, there are 20,046 subjects who have had their first time exposure to FluMist™. Please note that this includes 511 subjects from 50 to 64.9 years of age and 1254 were those subjects between 1 and 2 years of age. First I will begin with the adult experience with the representative trial being AV009, the healthy adult effectiveness trial.

A total of 3,041 FluMist™ recipients and 1520 placebo recipients were in this trial. REs and unsolicited adverse events were captured for seven days with 98 percent of subjects returning a diary card. SAEs were actively monitored with a phone call at 28 days post-vaccination. In addition, the sponsor collected any passive reported events after 28 days because, as you recall, there was a 5-month illness surveillance in the study. This shows selected RE

events by group, 3041 subjects with this number returning the diary card.

Both the FluMist™ and the placebo groups experienced at least one reactogenicity event, 70.9 percent in the FluMist™ group and about 62 percent in the normal allantoic fluid recipients. Runny nose and nasal congestion was the most frequent and recorded the greater than 10 percent difference between the groups. Sore throat was next, headache also occurred frequently though it's not on the trial.

And please note that the rate of fever was about 1 percent in both groups. Unsolicited or other adverse events are shown on this slide. Again, both the FluMist™ and placebo group were reactogenitic with any adverse event being reported in the 30 percent of the FluMist™ recipients and about 21.5 percent of the normal allantoic fluid recipients. Respiratory events occurred in 18.1 percent of FluMist™ and 7.5 percent of placebo. Allergic reactions, which had been a concern, were infrequently observed in either group.

And digestive events were also comparable between the groups. The only statistically significantly difference noted here was the occurrence of any adverse event. In study AV009, there were 46

subjects with asthma who were inadvertently enrolled with 23 of them being FluMist™. Though the numbers are small, there was an increase in REs noted in the FluMist™ and the placebo recipients who were asthmatics. For any adverse event for the placebo group, the rate was about 84 percent.

There were also 7 pregnancies noted in this trial. Five of them were FluMist™ recipients. There were 5 exposures in the first trimester which all led to full term live births, though I have no additional information for these pregnancies. There were also two spontaneous abortions, one each in the FluMist™ and the placebo group.

For the pediatrics safety monitoring I present AV006 years 1, 2 and 3. The REs were captured in this trial on diary cards for 10 days after each vaccination. Other adverse events were also collected for 10 days. SAEs were not actively monitored post-vaccination, though there were illness calls -- there were phone calls performed for illness surveillance. SAEs were not specifically queried. Selected REs are shown by group and by dose on this slide. As described earlier both the FluMist™ and placebo recipients experienced significant adverse -- any reactogenicity event occurring 74 percent of FluMist™

and 66 in placebo and 69 and 62 post-dose 2. Both of these were statistically significant with a p-value of less than .05.

Runny nose and nasal congestion was still the most frequent followed by vomiting and also we have myalgias and fever greater than 100.6 rectally. The sponsor presented 100 today but that was orally. This is the same fever categories. This was statistically different after dose 1 but not after dose 2.

This slide shows selected other adverse events by group and by dose. And adverse event was experienced by 18 percent of FluMist™ and 15 percent of placebo and a comparable rate after dose 1 and dose 2 and there was no difference between the study groups. Statistical difference were noted with abdominal pain occurring more frequently in the FluMist™ group after dose 1 and this was not seen after dose 2. Rash described as macular papular rash occurred more in the placebo recipients after dose 1 and it was infrequent after dose 2.

Again, allergic reactions was recorded and occurred infrequently after all doses in both groups. And respiratory events, which Dr. Mendelman listed today including pneumonia, bronchitis, sinusitis,

otitis, et cetera, were comparable between the groups in this display. In year 2 the reactogenicity events were shown to be similar in the subjects who had received 1 or 2 doses in year 1 after their re-vaccination in this year. Also there was no statistically significant difference for REs between the FluMist™ and normal allantoic fluid recipients. Both groups experienced -- 58 percent of both groups experienced at least one RE. And again, runny nose and nasal congestion was the most frequent, occurring in about 42 percent of both groups, followed by cough occurring in about one-quarter of both groups.

Of note, one 6-year old with a history of allergic reactions had hives and angioedema 30 minutes post-receipt of normal allantoic fluid, the placebo vaccine.

Safety monitoring was performed in the third year for these subjects called AV015. The subject who had completed years 1 and 2 were eligible for year 3 participation which was open-labeled administration of FluMist™. The subjects could have also participated in AV001, which means they may have previously received 1 to 4 doses of FluMist™. In this year the prior FluMist™ recipients were given one dose of vaccine and prior placebo recipients could

receive 1 or 2 doses separated by 28 to 60 days. There was day 42 phone calls to collect SAEs in this trial.

The reactogenicity events between the groups again, for runny nose and nasal congestion have the largest difference and as you can see, this occurred in 49 percent of prior placebo recipients compared to 37 percent of prior FluMist™ recipients after dose 1, which is essentially their first dose of receiving FluMist™ vaccine. No other differences and REs rates were greater than 10 percent. In looking at REs across 3 years of FluMist™, in year 1 approximately 73 percent of subjects experienced any RE. This decreased to approximately 56 to 58 percent in year 2 and year 3. Thus, there was no increase in REs observed with subsequent doses.

The sponsor also has continued to follow these subjects for a fourth year and those data are to be submitted to the BLA. During CBER's review of this file, pneumonia cases were identified and, thus, a search of all available data was performed. In year 1 looking at pneumonia within 21 days of vaccination, there were 6 FluMist™ and 1 placebo recipient which led to a relative risk of 2.98 with confidence intervals of .36 and 24.72.

For all cases not temporally limited, there were 8 FluMist™ and 2 placebo recipient for a relative risk of 1.99, confidence intervals of .42 and 93. Please note that one subject at Houston, who was diagnosed with pneumonia also had a culture positive for CAIV strain. In year 2, there were 2 FluMist™ subjects with pneumonia and these cases occurred at 15 and 68 days post-vaccination.

In the next study for safety, I will review the Kaiser trial briefly because it was presented in detail this morning. I will again emphasize that this is an ongoing review. In this trial SAEs and MAEs were monitored in 9689 healthy children from 1 to 17 years of age. The trial began in October of 2000. FluMist™ versus placebo in a 2 to 1 ratio was the design. Two doses separated by 28 to 42 days was for children from 1 to less than 9 years of age and one dose was for children 9 to 17 years of age. The data base was searched for MAEs and SAEs for 42 days after each dose.

And the data base was locked on December 31st for interim analysis for safety. At that time, which is the data that we have available at the CBER, approximately 89 percent of the 9 to 17-year olds had completed their post-dose monitoring and 68 percent of

the 1 to 8 year olds had completed their monitoring. The data was submitted to CBER on April 30th, 2001. The interim analysis included multiple comparisons as presented by Dr. Black. There were four clinical events that were pre-specified. These included acute respiratory events, systemic bacterial infections, acute gastrointestinal events and rare potential -- rare events potentially related to influenza.

The utilization setting was hospital, outpatient clinic, emergency department and combined and there was also stratification for age with these age groups of all 9 to 17, 1 to 8, 18 to less than 36 months and then 12 to 18 months. As mentioned, a total of 1500 statistical comparisons were performed without adjustments for multiple comparisons. Because of the large number there are some relationships that show differences that could have been due to chance.

From the interim analysis, 20 SAEs within 42 days were reported through April 15th of 2001. Thirteen of these are included in the FluMist™ group and 4 were within 14 days. This included hemolytic uremic, HUS syndrome in a 12-month old, acute gastroenteritis, AGE in a 14-month old, abdominal gynecological pain in the 16-year old female and appendicitis in a 15-year old male. All if these

events occurred on day 11.

In the placebo group there were 7 SAEs, 3 of them within 14 days. There was one croup in a 17-month old female that the sponsor coded as possibly vaccine related. Trauma in a 17-month old and a psychiatric disorder in a 12-year old and all of these occurred on day 4 plus vaccination. For MAEs within 42 days as of December 31st, 2000, 50 events were reported. These were not presented to you by study group. There were 20 percent that were coded as well-child or reassurance, 11 percent at URI and 7 percent for otitis media, trauma and psychiatric disorders. These codes are what's provided by the Kaiser provider on the sheets at discharge.

For interim analysis of pneumonia in 1 to 17-year olds, less than 21 days post-vaccination, interim there were 10 FluMist™ group and 6 in the placebo group for relative risk of .83 with these confidence intervals of .3 and 2.28. For all cases identified the sponsor presented 14 FluMist™ and 10 placebo with a relative risk of 0.7 with confidence intervals of 0.3 and 1.57.

As you recall in AV006, the subjects were 15 to 71 months of age. An analysis in this study by age group is ongoing. The sponsor reviewed these this

morning so I will briefly point out MAEs that they have assessed as plausibly related biologically to FluMist™ with an increase in the FluMist™ group compared to placebo. Conjunctivitis that has been described increased in 1 to 17-year olds, 1 to 8-year olds and 18 to 36-months old and seem to have a temporal relationship.

URIs were also increased from 1 to 17-year olds. Abdominal pain, musculoskeletal pain was also increased in 1 to 8-year olds and the 18 to 36-month old. Asthma in 18 to 36 months was 7.75 events compared to zero events per 1,000 person months in the placebo group and the otitis media with effusion in 1 to 8-year olds in the clinical setting post-dose 2 as described by Dr. Black this morning or earlier this afternoon.

They have also -- it seems like this morning, I agree. A long day. In the Texas community study, AV012 trial, this is a 1-dose of FluMist™ given to children 18 months to 18 years primarily performed in Scott and White HMO in Temple/Belton, Texas to assess effectiveness against medically attended acute respiratory infection. For this BLA, SAEs within 42 days were reported. Reporting methods included postcard reporting with reminder calls and

also there were data base searches performed for 79 percent of the subjects who had their primary health care at Scott and White.

There is also a collection of passive reports from the parents of the subjects of any concerning adverse events to them. There were 531 of 4298 subjects identified to have asthma, reactive airway disease or wheezing which was not an exclusion in this community trial. The SAEs and captured other AEs are shown on this slide. There were 8 SAEs with 6 of them occurring more than 21 days post-vaccination. There were 149 out of the 40,063 subjects who had 42 data available that reported onset of at least one new illness.

Eighty-seven of these events and 78 subjects were judged by study personnel to be clinically significant. After being considered clinically significant they were recorded on a case report form and entered into the data base. On FDA review of these 9 listings 65 were respiratory events and 10 diagnosis of pneumonia and/or bronchitis were identified. This also is an ongoing analysis and the full data set has not yet been presented to CBER, including the analysis on asthmatic subjects.

For the subjects that had completed the

trial, I believe it was 409 asthma subjects, there was not an increase in medically attended respiratory events. These are preliminary data. As I mentioned, because of the risk of inadvertent exposure in high risk subjects, some studies have been done, including AV010, which was the asthmatic trial. Forty-eight subjects with 24 FluMist™ and 24 placebo recipients, 9 to 17-years of age with moderate to severe asthma were given one dose of study vaccine. The subjects were monitored for safety, tolerability and asthma stability for 35 days, including 7 days pre-vaccine to establish their baseline and 28 days post-vaccination.

This shows the adverse event profiles of the subjects and, again, please note the both the FluMist™ and normal allantoic fluid were reactogenitic with 91 percent of both groups experiencing at least one RE. Runny nose was the most common with 75 percent and 56 percent of the groups. Cough occurred in about 40 to 45 percent. Fever was more frequent in the placebo recipients. Two subjects or 8.3 percent experienced an asthma exacerbation meaning a required increase in medication or therapeutic intervention but none of these required hospitalization and there are no SAEs reported in this trial.

Briefly, I will review the HIV trial. There were 57 HIV infected subjects and 54 HIV negative subjects who received FluMist™ or placebo vaccine in a 1 to 1 ratio. There was one HIV subject who shed cold-adapted influenza virus, Type 9 on day 5 post-vaccination but was culture negative on day 7. AEs were comparable in the two groups, occurring in 12 to 16 percent of HIV positive and HIV negative subjects.

CV4 counts decreased 8 percent in the HIV positive FluMist™ recipients transiently at day 28 and had increased by day 90. There was no increase in viral load post-vaccination and these subjects were followed for 6 months.

A Veterans Administration Study was performed and the study synopsis is provided in the BLA. In this study, they evaluated 22015 adults more than 50 years of age with chronic obstructive pulmonary disease. The subjects received 1 dose of FluMist™ or placebo in a 1 to 1 ratio given concurrently with TIV. Only SAEs were reported in March of 2001 which included 63 deaths in this trial, 34 in FluMist™ and 29 in placebo recipients. Approximately 8 deaths, four in each group, occurred within 28 days of vaccination. As I mentioned

earlier, an increase in pneumonia was noted in AV006 and so we searched all available data at CBER for pneumonia cases. These are CBER generated data and include review of inspection reports, data base, line listings and any SAE reports from the sponsor.

I have not totalled this column on purpose because there are varying follow-ups and varying dosing regiments and varying capturing for AEs. To date we have identified 37 pediatric cases after FluMist™ of pneumonia. Actually, we have 2 additional ones since I prepared this slide and also 12 cases of placebo -- 12 cases of pneumonia identified in placebo. The data that's most useful are in studies AV006 and AV019 where there are denominators. However, AV019 is an interim analysis and the final data set has not yet been analyzed.

In AV006, as I presented earlier, for pneumonia less than 21 days the relative risk was 2.98 but there was not an increase in relative risk noticed in study AV019 in 1 to 17-year olds. So in CBER review of pneumonia, the things that we would like you to note is that there was one death that occurred in pneumonia as described by Dr. Mendelman. Symptoms began 23 days after the second dose of FluMist™ in an 18-month old boy in a live sponsored trial in South

Africa.

There was also one pneumonia case identified by CBER inspectors which occurred 15 days post-dose 3 in a four and a half year old in year 2 of AV006. The parents reported this to the study site a year after it occurred and there was one case of pneumonia that was associated with culture positive CAIV. For deaths, there was 65 deaths reported, actually it was 66 because I have left off the one child who died of a brain tumor as described earlier. The one pneumonia case -- there was one adult who died from accidental drowning associated with alcohol intoxication and there were 63 deaths in the VA study which I cannot describe in more detail.

So our conclusions is our review is ongoing. Our review of respiratory events, including pneumonia and search for a diagnosis of bronchitis and bronchiolitis is not complete. FluMist™ and the normal allantoic fluid placebo are reactogenitic. Most of the safety data in this BLA have been generated in trials of healthy subject. There have been a few high risk subjects evaluated and there is a suggestion of increased REs and asthmatics. There was no increase in REs noted with annual dosing of children and also there were a few subjects evaluated

at either end of the age spectrum.

Additional concerns are concurrent immunization. At this time, there are no data for safety or efficacy with concomitant immunization, including traveler's vaccine available in any age group. For transmissibility, the Finnish trial has been presented but the full data set has not yet been reviewed but there was note of one subject who was a placebo recipient that shed vaccine virus.

And also we have no data for the annual revaccination of adults. Thank you.

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

DR. MINK: And since it's late, no questions.

CHAIRMAN DAUM: And since it's late -- no, wait a minute. I'd like to open the floor now to committee for questions and clarification of Dr. Mink's presentation. Dr. Eickhoff, then Dr. Edwards.

DR. EICKHOFF: Dr. Mink, you described very nicely the curious events in Houston with positive cultures for CAIV in those first 10 days with a curious association with illness, both fever and CDC-ILI. But you refrain from speculating as to what might be going on here. Would you speculate at this