could, please share with us your thoughts about the over 65 group.

DR. CONNOR: Yeah. I think, you know, obviously we focused our attention on the healthy individuals that are within the age group that could, if the vaccine was provided, could enhance the vaccine uptake in the healthy population, and once we've studied that population, then in addition we'd like to be able to study the vaccine in other higher risk populations, including the elderly population, as well as other patients.

So there are clearly plans and desires to look at that population. Obviously out focus has been on the healthy population principally.

DR. EICKHOFF: Thank you.

CHAIRMAN DAUM: Dr. Myers, please.

DR. MYERS: In follow-up on that and Dixie's question, this is a vaccine that at least on the current indication is not indicated for any of the high morbidity risk groups, and in a way, that makes the safety bar go higher, it seems to me.

And so I have two issues. The first one is that although it's intended for healthy individuals, it's likely to be administered to those who have unrecognized immune deficiency,

unrecognized pregnancy in smokers. It's likely to transmit to the elderly in family settings and to younger siblings.

And so I guess I have some questions about safety in those groups and would ask if you could address some of those.

And then a second thing is I'm struck by the fact that in all of your studies about 20 percent of recipients of normal allantoic fluid intranasally require anti-pyretics. Forty percent of adults have headaches, basically have febrile URI after getting normal allantoic fluid.

And I remember at the last meeting raising the question has normal allantoic fluid been compared to a placebo for reactogenicity, and again, is this a vaccine intended for the normal host, normal healthy adult?

I think we need to ask why there are so many febrile URIs in the placebo group.

DR. CONNOR: I think to take the second question first, normal allantoic fluid has been used as the control group for most of these studies and other CAIV studies mostly obviously for the placebo, for the masking effect and other effects.

We have looked in several settings, and

I can either show slides or show slides later of the distribution of the placebo activity. If you look at the distribution of the URI symptoms, for example, after a dose of placebo, you see no temporal distribution associated with giving the normal allantoic fluid.

The other fact is that there are some studies that Wyeth has conducted using saline placebo in the same setting, and what you actually see is the healthy patient effect. What you see is that you're screening out patients before they get vaccinated, and then both in the FluMist and in the placebo groups or in the other cases in the FluMist and the saline group, you see regression basically back to what is the normal rate of respiratory symptoms in adults in that population.

So, for example, you see return back to about 20 percent of children having URI respiratory symptoms. So the evidence actually suggests that what's happening is that the base population rate is what you're actually seeing with normal allantoic fluid, and the reason why there may be some trend is that the trend is basically screening out the healthiest patients right before you're doing the vaccination.

And I can either show some of that information or not, but the other issue is that we obviously have focused, as I mentioned, our attention primarily on the healthy individuals. There have been some studies that have been done on some immunocompromised host populations, a relatively small study that was done in HIV infected adults in which there was nothing of interest in terms of significant disease in that population, and that's the primary extent of the population that we studied thus far.

CHAIRMAN DAUM: Okay. We have Dr. Markovitz and Diaz, and again, we're looking for input on clarification of what the presentation consisted of at this point, with time to return to many of these important issues a little later.

MR. MARKOVITZ: Yeah, I have two questions. One, it seems as though -- and this sort of follows up on some other questions asked -- it appears that COPD patients, for example, would be an obvious eventual target here, and I understand you're not asking for an indication here, but have they been studied and you've seen similar things that you've did as seen with kids vis-a-vis asthma or is this something that has just not been studied

at all thus far?

DR. CONNOR: Yeah, the only studies that have been conducted at studying COPD and the VA studies that are not part of this application in which COPD patients -- I think part of that data was mentioned the last time at the last VRBPAC -- in which there are some analyses of that trial, including some adverse event outcome. It wasn't anything specific that was seen in terms of serious adverse events or other outcomes in the COPD patients that were different, although obviously the rates of illness in events were higher than in the healthy population.

MR. MARKOVITZ: So there's some data, but not conclusive at this point.

DR. CONNOR: Right.

MR. MARKOVITZ: The second question is it appears that a lot of the studies are done in a rather homogeneous population. Do you have any information in terms of like inner city populations or anything like that?

DR. CONNOR: Yeah, i think we can show you data later about the geographic distribution and the demographic data distribution of the populations. We see no difference based on

background, ethnicity, racial distributions, age distributions, et cetera, and we can show you some of that data later if you are interested.

CHAIRMAN DAUM: Dr. Diaz.

DR. DIAZ: I had just a few quick questions. I, too, was struck and concerned about the difficulties of diagnosing and/or labeling younger children with asthma as a diagnosis and was wondering in the studies on asthma and wheezing if additionally you looked at the use of any pharmaceuticals in the population, i.e., bronchodilators or other indicators of concern in wanting to treat true wheezing episodes.

DR. CONNOR: Yeah, I think the data that we have from the first study which looks obviously at a generally health population, but populations that still got into the study that had something in their medical records that were associated with asthma and wheezing; we did look at those individual events for what happened to them.

And while one of the kids were hospitalized, as most kids who have asthma and wheezing events, they were treated with various kinds of medications, including brochodilators, and about 20 percent of them some steroid use.

That was generally distributed primarily in patients that had true diagnosis of asthma. In the general population we didn't specifically go back and look independent of anything else whether there was --

DR. DIAZ: That's what I was wondering.

DR. CONNOR: -- yeah, whether there was asthma diagnoses.

My sense is from looking at that data, however, is that there's pretty good correlation between anything in the record that says anything about wheezing, which is basically what we're culling out, and the use of bronchodilators in general.

DR. DIAZ: Additionally, I just wanted to clarify in your efficacy studies. I seem to recall looking at efficacy out to 42 days. Am I incorrect in that or was that the endpoint?

DR. CONNOR: Yeah, the follow-up period was generally through 42 days, and it was all culture confirmed influenza in the outcome.

DR. DIAZ: So you don't have --

DR. CONNOR: I'm sorry. You're referring to the efficacy outcomes rather than the safety outcomes.

DR. DIAZ: Correct.

DR. CONNOR: Which are through the whole season, yeah.

DR. DIAZ: Which is through the whole season?

DR. CONNOR: Efficacy.

DR. DIAZ: Efficacy. That's what I wanted to clarify.

DR. CONNOR: Yes.

DR. DIAZ: Because that's a very important point.

DR. CONNOR: Yes.

DR. DIAZ: Additionally, the issue about transmission, I think, is an important issue. Are there any markers other than the attenuation markers as such that you can follow resorted strains if, in fact, you did revert to that worst case scenario that somebody described of reverting or resorting to the wild type strain? Would there be any genetic markers that could still predict that that particular strain had resorted from the attenuated strain that you know of?

DR. YOUNG: Yeah, basically what you have to do is there are ways tat we can either sequence or do RFLP analysis of the strains to

follow that.

In fact, within that Finnish day care study looking at the viruses shed from the vaccinated individuals, we could actually, because there were a single point mutation differences, you know, that are silent mutations between the cold adapted strains so that we could actually show that there were four reassortant events that occurred between the H1N1 cold adapted virus and the H3N2 adapted virus. So you can actually follow whether the genes do get switched, but again, we've never seen any change in phenotype when that happens.

DR. DIAZ: Right, and lastly I just wanted to ask, and I presume you don't have any studies that look at transmission in a household setting?

DR. YOUNG: We have not done that with CAIV that I'm aware of. I guess there were some -- Paul, there were historical studies done with CAIV?

Paul Mendelman.

DR. MENDELMAN: In the briefing document that we provided, the ten publications for transmission studies were done historically with predecessors of FluMist, and those included various settings, including households and college roommates

as well as children and adults and married couples.

CHAIRMAN DAUM: Okay. Thank you very much, committee members. Thank you sponsors for your presentation.

It is 10:45.

Dr. Mendelman wishes to inform that in those studies no transmission occurred.

(Laughter.)

CHAIRMAN DAUM: It's 10:45 here in the Eastern time zone, an we will take a ten minute break and reconvene at 10:55.

(Whereupon, the foregoing matter went off the record at 10:48 a.m. and went back on the record at 11:00 a.m.)

CHAIRMAN DAUM: Will everybody please take their seats so that we can begin?

I'd like to continue our meeting by calling on Dr. ChrisAnna Mink of the FDA to give us the FDA presentation.

If everybody could take their seats and cease conversations as quickly as possible so we can get moving on the committee's agenda.

Dr. Mink.

DR. MINK: I'd like to now begin the FDA clinical summary for the FluMist application.

You've heard much of this this morning. So will try to abbreviate where I can.

A total of 20 studies have been submitted to the biologics license application. Fourteen were randomized, double blind, and placebo controlled, and three of these were considered to be pivotal safety trials. They were randomized two to one, FluMist to placebo. There include 06, the efficacy trial; 09, the adult trial; and 019, the large safety trial for Northern California Kaiser.

There are also six non-placebo controlled trials.

Final reports for three of the 20 trials were submitted with the sponsors' responses in January 7, 2002, and have not previously been presented in full to the committee. These include 019, the Kaiser trial; 012, Texas community trial performed largely in a health maintenance organization; and the Wyeth-Lederle sponsored transmissibility study in day care.

A total of 20,228 first doses of FluMist have been given, and in the age range requested of five years through 64 years, 14,154 first doses have been given.

I would now like to review the trials

recently submitted. We'll start with the 019 Kaiser trial.

This enrolled healthy children from one to 17 years of age, randomized two to one, FluMist to placebo; two doses, 28 to 42 days later for the one to eight year olds groups and one days for nine to 17 years.

It started in October of 2000, and they used the 1999-2000 vaccine strain for this safety profile. Both of the A strains differed from 1999 on 2000 season, though there was some similarity, and the B strain was the same.

The exclusion criteria listed was the parental reported history of asthma or possible asthma.

In this trial, there was no active monitoring for solicited reactogenicity events plus vaccination, events such as cough, fever, or runny nose.

The Northern California Kaiser database was searched after each dose for their primary safety outcomes listed here. Serious adverse events were defined consistent with 21 CFR, including death, life threatening, hospitalizations, significant disability or congenital anomaly or

birth defect.

Medically attended events were defined as an encounter with the health care provider. There were 170 individual events searched and four prespecified groups categories.

You've heard this earlier. The four prespecified categories were acute respiratory events, which included approximately 25 diagnostic codes; systemic bacterial infections; acute gastrointestinal events; rare events, historically associated or you'll see coined potentially related with wild type influenza.

The utilization settings include hospital, out-patient clinic, emergency department, and all settings combined.

Prespecified age groups were 12 to 17 months, 18 to 35 months, one to eight, nine to 17, and then all age groups one to 17 years.

Statistically the plan was to estimate incidence of MAEs and SAEs in the FluMist recipients relative to the placebo subjects in the post vaccination period. This is expressed as relative risk, RR, in 90 percent confidence intervals constructed using the binomial method.

Multiple encounters for the same MAE

were counted only one. Ninety percent confidence intervals were used for these safety assessments.

Interim analysis was performed with unblinding to provide safety data at VRBPAC 2001. Over 1,500 analyses were performed, and there were no adjustments for multiple comparisons.

A total of 9,689 evaluable subjects were available. This included a 6,473 FluMist and 3,216 placebo subjects. Approximately 8.5 percent of participants had a history of asthma upon review of the database and medical records. Approximately 75 percent of those subjects were from one to eight years of age.

As you can see, the age distributions for those one to eight years were about 58 percent of enrollees and about 42 percent were nine to 17 years. There were similar demographic characteristics for age, gender, and ethnicity in the two treatment groups.

Eighty seven percent of the one to eight year olds received the dose two of their vaccine regimen. The reasons provided for not receiving dose two included unable to contact, which was about 55 percent of the FluMist subjects, or noncompliance, which was about 35 percent in FluMist

subjects.

Adverse events following dose one were reported as the reason for not returning for dose two for 39 FluMist subject and 27 placebo subject. In the line listing of these adverse events, most appear related to the respiratory tract.

The results for the SAEs are shown on this slide. No deaths were reported. A total of 20 SAEs were reported with the rate of .02 percent for both groups, FluMist 13, placebo seven subjects.

Of the 13 SAEs in the FluMist subjects, 12 were reported after dose one. These events included 11 hospitalizations, six psychiatric hospitalizations, and three others, such as an ED visit, one clinic visit, and an out-patient surgery. There were no patterns for the diagnosis seen for SAEs.

The next slide shows the number of subjects with medically attendant events by setting. As you can see, clinic visits were the most common, occurring in about 36 percent of both groups.

Hospitalizations were infrequent, occurring in less than .6 percent of both the FluMist and placebo subjects.

For the prespecified group diagnoses,

none of the groups had occurred at significantly increased rates in the FluMist recipients. There were no reports of systemic bacterial infections and no relative risk could be calculated.

There was a decrease in the relative risk, significant for acute respiratory events in the FluMist recipients for all ages, settings, and doses combined with the upper bound of the relative risk confidence interval being less than one.

The results for asthma events, overall the asthma events occurred in approximately .4 to 1.3 percent of FluMist recipients, depending upon the age groups evaluated. In the interim analysis presented at VRBPAC last year, there was an increased relative risk for asthma events observed in FluMist subjects ages 18 to 35 months, one of the prespecified age groups.

In the final analysis, this increased statistically significant increased relative risk was still observed in the 18 to 35 month age group.

As shown on the next slide, for all settings following dose one in 18 tc 35 month old children there were ten events, ten subjects in the FluMist group and zero in the placebo with a lower bound of 1.95. For all settings and all doses

combined, the relative risk was 4.06 with these confidence intervals.

The NA -- I hope you can read the footnote -- means not available, not able to calculate due to zero events occurring in the placebo subjects.

This slide describes the asthma events in the 18 to 35 month old children. There were a total of 18 subjects, 16 FluMist and two placebo, that had 20 asthma events. Seventeen of these subjects were seen in the clinic, and one subject was seen in the emergency department, and this was following dose one.

All subjects required treatment with 94 percent of them receiving beta agonists.

To help further evaluate the age related risks for asthma a post hoc analysis was performed by the sponsor looking at subjects in increasing six month increments, starting at 12 months of age through 107 months of age. Selected age groups for this analysis is shown on this slide. Here's the 12 to 35 month old group, but we stop at the 77 month.

As you can see, there's an increase relative risk of 3.53 identified for the 12 to 59 month age group, with the lower bound of 1.1 in

these upper bound confidence interval.

The statistically significant risk was not identified for age groups over 12 to 59 months of age. This slide shows this analysis for the 12 to 59 months after dose one with the increased relative risk. This is a CBER generated table. So the confidence intervals are a little different because a different calculation method was used.

After dose two the relative risk was not significantly increased and subjects 60 to 107 months of age after dose one or dose two, there were no increased risks identified, nor was there an increased risk in nine to 17 years of age.

To summarize, for asthma events the increased risk was 3.53 for the 12 to 59 months after dose one, not seen after dose two, or in the 60 to 107 month or children nine to 17 years of age.

Upper respiratory infections were also evaluated. There was no increase in the relative risk for URI in combined analysis of all ages, settings, and doses. There was one SAE and a placebo recipient for hospitalizations for URI and croup observed on day four post vaccination.

There was an increase in the relative risk for URI in three of the 41 separate analyses as

shown on the next slide. The sponsor also showed these data to you earlier.

You can see there was an increase in the entire cohort in the emergency department after dose one with the lower bound of 2.14. No events occurred in the placebo group.

The events in the one to 17 years were primarily accounted for by subjects in the one to eight, with nine events here and 11 here. Again, the lower bound was 1.7 with no events in the placebo subject.

There was also an increase identified in 18 to 35 month old subjects for all doses and all settings combined with a relative risk of 1.3.

Pneumonia events were also evaluated, and in that search there was no increase in the relative risk observed for pneumonia, bronchitis or bronchiolitis in any age group, setting, or dose observed. I will discuss this in a bit more detail later.

Additionally, a search for abdominal pain was performed. This occurred in about .7 percent of FluMist and .8 percent of placebo subjects. There was an increased relative risk in two analyses, in the nine to 17 year olds in the

emergency department and one to 17 years in the ED, and there was a decreased relative risk in two analyses, one to eight year olds in the clinic and one to eight year olds in all settings following dose one.

There were no specific abdominal disorders identified and no cases of intussusception, mesenteric adenitis, or intestinal obstruction were reported.

A search for rare events potentially related to influenza show that there were no cases of encephalitis, encephalopathy, Guillain-Barre, Reye's Syndrome, or other influenza associated disorders.

There were ten subjects, seven FluMist and three placebo, who reported 11 seizure events. Five of the seven FluMist subjects and one of the placebo subjects was less than five years of age. As you can see, the relative risk was not increased for the events of seizures.

So in conclusion, for this trial AV019 was the major contributor to the safety database, especially in the pediatric age group. SAEs occurred at a rate of .2 percent, and there were many children with asthma enrolled, despite

exclusion criteria.

There was an increased relative risk for asthma in the 18 to 35 month olds after dose one in the prespecified age groups and in 12 to 59 month olds in a post hoc analysis. The children with asthma events did require medical therapy.

No significant increase in relative risk for asthma was observed for children over 60 months of age. There was no increase in the relative risk for pneumonia identified, nor were there rare events possibly related to influenza reported.

An increased relative risk for URI events and musculoskeletal pain, which was presented earlier by the sponsor, was observed in children 18 to 35 months of age, suggesting that possibly these children upper respiratory infections or mild influenza-like illnesses.

There were 1,500 analyses performed in this trial, and an increase for some of the relative risk for some of the MAEs may be due to chance alone. Additional studies are needed to assess the association of asthma events following the receipt of FluMist.

The next trial that will be discussed is Study AV012, the Texas community trial, and I will

discuss years one and years two.

The design was open label, nonrandomized, and the children were 18 months to 18 years of age who were eligible for participation, and children with a history of mild asthma were permitted in this trial.

The vaccine, each year that the kids were enrolled, they received a single dose of FluMist. The study was planned to assess herd immunity following FluMist and safety monitoring was a secondary objective.

There were several limitations for the design of this trial, and effectiveness data will not be discussed. We are presenting only the safety data from years one and years two. These data contribute the safety experience following 9,549 doses in 7,448 children.

For the revised plan for safety assessments, which was implemented after the trial was initiated, SAEs for 42 days post vaccination became the primary measure of safety. These were captured by postcard reporting of database searches.

Medically attended acute respiratory illness, MAARI, became the secondary measure of safety. These were captured by database searches

for overall MAARI events and for selected respiratory events, including asthma.

Data analysis of MAARI events used the post marketing method described by Griffin, et al. Each participant served as his own control. Event rates within a specified vaccination period were compared to event rates within a reference period. There were two vaccination periods: day zero to 14 and day zero to 42.

A single reference period was constructed by combining pre-vaccination period and a post vaccination period. The results show that in year one the study period was from August 17th, 1998, through January 30th, 1999, and 4,298 subjects were enrolled. Approximately 13 percent of these had a positive history for asthma.

In year two, the study period was September 13th, 1999, through February 10th, 2000. Fifty-two hundred and fifty-one subjects were enrolled, and the asthma history was positive for about 17 percent of subjects.

A total of 2,101, or about 40 percent of the subjects, were repeat vaccinees.

SAE results. There were no deaths reported. In year one there were eight SAEs and the

4,131 evaluable subjects were a rate of .2 percent. Six of the eight SAEs occurred beyond day 21. The two that occurred within 21 days included hospitalization for depression in a 16 year old and aseptic meningitis in a seven year old.

In year two there were 16 SAEs, all hospitalizations, reported in 15 of the 5,033 evaluable subjects for a rate of .3 percent. Nine of the 16 occurred on or after day 21. Two SAEs were related to the respiratory tract, and this included on day 11 in a 23 month old, who was admitted for RSV documented pneumonitis and febrile seizure, and on day 44 post vaccination an event of pneumonia in an almost four year old.

There were generally multiple different diagnoses included in the SAEs for year one and year two, and no pattern was observed.

MAARI results, in brief. There was no increased relative risk for overall MAARI for either vaccination period observed in year one. In year two, there was an increase in MAARI events for both vaccination periods, day zero to 14 and day zero to 42, as shown on this slide.

Asthma events overall were reported in approximately one percent of all participants in

each year one and year two. In year one there was no increase in the relative risk for asthma events for either vaccination period. In year two, no increase was observed from the day zero to 14 period, but there was an increase in asthma events for day zero to 42 with the relative risk of 1.83 and those confidence intervals.

There are several limitations to this trial, including that it was not randomized or blinded. No control group was available for statistical comparisons, and the post marketing method used for the data analysis may be problematic for evaluation of pre-licensure safety.

For example, the method has most often been used for acute events, not chronic events, such as asthma, and has not been previously used for events associated with seasonality, such as influenza.

The MAARI evaluations for safety were not prospectively defined, and as you saw in the data, there were differences in MAARI rates observed between years one and years two.

Conclusions from this trial were that 7,448 subjects received 9,549 doses of FluMist, which is approximately 37 percent of the total first

doses observed in our safety data base.

The rates of SAE were .2 to .3, which was very similar to the rates observed in AV019, the randomized, double blind trial.

There were no reported events potentially related to wild type influenza. There was an increased relative risk from MAARI observed in some analyses, but not in others.

Briefly to compare AV012 and AV019, the rates for asthma events were similar in the two trials, between .5 and 1.5 percent for FluMist recipients, and this occurred despite the marked differences in the design of the trials, most notably one being open label versus randomized double blind.

To further evaluate the asthma and wheezing events, the sponsor performed a review across all 20 trials in the BLA. As they discussed earlier, there was significant overlap in the use of the diagnostic codes for asthma, reactive airway disease, RAD, wheezing, and shortness of breath, SOB.

So across these 20 studies, approximately 82 to 80 percent of asthma RAD, wheezing, and SOB events, and 74 percent of asthma

RAD occurred in children from one to nine years of age. This age group accounts for approximately 50 percent of the total study population.

Asthma events occurred throughout the 42 day post vaccination period with no clear evidence of temporal clustering.

A search of SAEs related to asthma, there were four hospitalizations identified for the grouped category. In AV006, year two, a 23 month old with a history of asthma was admitted for status asthmaticus on day eight after dose three of FluMist. In 008, an adult, a 69 year old with heart disease, wheezing, and congestive heart failure, was admitted on day 16 post FluMist. And in 02, a child had two hospitalizations for RAD on day four and day 33 in a placebo subject also with a known history of asthma.

This slide shows the occurrence of events for the protocol defined age groups. In 06, that was 15 to 71 months after dose one. There was no increase in relative risk. In 019, one to eight after dose one, no increase, statistically significant. In 019, in nine to 17 years, there was no increased risk, nor was there an increased risk seen in adults.

These are for, as I noted, the predefined age groups in the protocols. However, in the analysis by age subgroups, as discussed above in AV019, there was an increase observed for 12 to 59 months of age and for 18 to 35 months of age. AV019 was the major contributor of children to the database, and thus the review of the 20 studies is very similar to these results.

Study 010 was also performed, which enrolled nine to 17 year old subjects with moderate to severe wheezing. Three of 24 FluMist recipients compared to zero of 24 placebo recipients had exacerbations in the 32 days post vaccination in that trial.

Thus, the concern is ongoing for the risk of asthma and wheezing in young children and possibly for subjects with a known history of asthma.

The third trial that we will discuss is the Wyeth-Lederle vaccine sponsored trial D145, which is assessment of the transmissibility of CAIV-T, FluMist, in day care attendees in Finland. This trial was randomized one to one, double blind to assess shedding and transmission of cold adapted influenza vaccine on strains in day care attendees

who are eight to 36 months of age. They were eligible to participate in the study if they attended day care at least three times a week for at least four hours per day. There had to be at least four contacts in the play group with at least one vaccinee within that play group.

The subjects were given one does of cold adapted vaccine or placebo. Then nasal swabs were obtained in day zero, day one, and three alternating days, such as Monday, Wednesday, and Friday, per week through day 21.

Isolated vaccine viruses were typed, A or B, subtyped, H1N1 or H3N2, phenotyped for the cold adapted and temperature sensitive, and a subset was genotyped.

The original primary objective was to assess the percent of placebo subjects who were shedding virus identified as vaccine strains.

And the sponsor's post hoc analysis, using the Reed-Frost model, was to assess the probability that a vaccinee would infect a placebo subject.

A total of 197 subjects, 98 FluMist and 99 placebo, were enrolled from 51 day cares as the sponsor described for us earlier. A typical play

group included two CAIV and two placebo recipients, though there were a lot of variations.

The all available shedding population, i.e., the assessment of shedding, could be performed from all 197 subjects. I present here for you the FluMist results. Eighty percent of the FluMist recipients shed at least one vaccine strain. Forty-three shed Type A; 72 shed Type B; six shed Types A and B; six shed all three types; and there were 13 subjects who shed viruses that were not able to be subtyped or genotyped. This included six Type A and seven Type B.

The duration for shedding is shown on this slide. For the H1N1 there were 33 isolates. All were vaccine strain. There was no H1N1 circulating at that time is my understanding in Finland.

The median day for shedding for H1N1 was three, but the range was one to 21, and as you'll recall, 21 was the last day cultures were obtained.

For H3N2 there were 12 isolates. Median shedding was eight days with a range of three to 17, and for Type B, there were 72 isolates, 65 confirmed as vaccine strain, and the range of shedding was one to 15 days. There were no wild type isolates

recovered from FluMist recipients during this trial.

For the transmission assessment, the placebo subjects included 93 available. This excludes six subjects who had no contact with the FluMist vaccinee. The all evaluable population defined by no protocol violations included 57 subjects. No protocol violations mean that they were not outside of the eight to 36 months of age; that they had nasopharyngeal cultures obtained less than four days. They had at least contact with one cold adapted recipient, and that there were at least four subject in their play group.

From these placebo subjects, viruses were recovered from seven subjects. One subject shed Type B Ann Arbor vaccine strain identified on day 15. Six placebo subjects shed a total of nine Type A isolates. Two subjects shed wild type on two different days, a total of four isolates, and four subjects shed a total of five isolates that could not be identified.

That's really hard to say.

For the subjects that had transmitted Type B vaccine virus, this subject was identified to be shedding on Day 15. He had at least ten other negative cultures obtained on other days.

The subject did have contact with two cold adapted recipients who were known to shed Type B. The B Ann Arbor isolate detected from our placebo recipient was detected five days after the last identified shedding by the vaccinee. This placebo subject had coryza on days eight or 18, cough on days eight or nine, and irritability on day zero, 14, and 17.

Essentially this reactogenicity profile was similar to direct recipients of cold adapted vaccine.

The probability of transmission is provided on this slide by the original analyses, including isolates identified as vaccine virus equals one, the Type B, among 57 eligible placebo subjects. The rate of transmission is 1.75 percent with those confidence intervals of .1 to 8.75 percent.

For the all available transmission of 93 subjects, assuming that all subjects with unidentified virus had vaccine strain, that would be an N equals five. The rate of transmission would be 5.38 percent with those confidence intervals.

To try and help correlate this with the Reed-Frost, this placebo subject had contact with

two vaccinees. The Reed-Frost data presented by the sponsor, the rate of transmission was less than one percent per vaccinee. So a rate of 1.75 for two vaccinees, it's fairly comparable.

Genotype was performed on selected shed isolates. They were chosen for genotyping if the culture grew a single virus subtype, if it had a viral content of 100 to 1,000 infectious foci, and the sponsor also chose later isolates to try and increase the chance of identifying nucleotide changes.

The consensus genomic sequence of the isolates from all placebo subjects and the subset of FluMist subjects were compared to the sequences of the relevant monovalent viral harvest, i.e., H1 was compared to H1, et cetera.

The B Ann Arbor transmitted isolate had three nucleotide changes identified. Fifty-five of a possible 237 isolates from FluMist subjects were tested, and nucleotide changes were identified in 76 percent of H1N1, 92 percent of H3N2, and 77 percent of B.

Of note, the B isolate with these nucleotide changes was found to be identical to the B isolate recovered from the vaccinee.

Genotype and phenotype stability showed that the nucleotide changes were not random, but look at H1 and H3N2 together because they have the same internal donor gene sequence. So for Type A, the changes were most commonly identified in PB1, 2, NP and the M genes, and for Type B they recurred in the M gene.

All of the tested isolates, N equals 55, maintain their attenuated, cold adapted and temperature sensitive phenotype. Evaluation of the retention of attenuation of the shed viruses in the animal model is ongoing.

In conclusion, there are several limitations for this trial. Despite its labor intensive nature, it is a small sample size and there were many protocol violations. Shedding of vaccine virus was frequent, occurring in about 80 percent of subjects and lasted through day 21, which was the last day cultures were obtained.

Transmission did occur. However, we can estimate only accrued rate. The recovered vaccine viruses had a high frequency of nucleotide changes. However, the cold adapted and temperature sensitive phenotype markers were retained. These changes were not random, but the clinical significance is not

known and evaluation of the attenuation in animal models is still ongoing.

Additional assessments of shedding were also performed by the sponsor. In four trials routine cultures were obtained from day zero to ten post vaccination. Of those 569 cultures, about 34 and a half percent of the subjects were identified to shed vaccine virus, and illness cultures were obtained from about 13.8 percent of those. Forty of 290 cultures obtained from FluMist subjects with illness post vaccination were identified to shed any influenza virus, i.e., its type not identified.

Twenty of those 40 isolates were tested by genotyping and phenotyping, and of those tested, they proved to be vaccine strain.

And the genotype and phenotype stability of the strains recovered from the ill subjects, of the 20 vaccine strains isolated from these ill subjects, none were reported to have altered their cold adapted or temperature sensitive phenotype. As most of these trials were performed when wild type influenza was circulating, primarily H3N2 and B, there's no resortment of vaccine strains and wild type were not identified.

I briefly will review the selected data

for post vaccine solicited reactogenicity events. The sponsor gave you much of this data this morning, and I will do a very brief summary from 06 and 09.

The selected REs included runny nose, nasal congestion, sore throat, cough, irritability, headache, chills, myalgia, decreased activity, and fever.

The events were solicited for ten days in 06 and seven days in 09, the adult subjects.

I have selected only a few events, and I chose the ones that were statistically different between FluMist and placebo in dose one for children 15 to 71 months of age in AV006.

As you can see, any RE, that is, the subjects had one or more reactogenicity event, occurred more than 60 percent of the time for FluMist subjects and placebo subjects after dose one and dose two.

Runny nose was significantly different as were vomiting myalgias, and low grade fever. After dose two, generally speaking the rate of reactogenicity events were a bit less common.

In year two no statistically significant differences in REs between the FluMist and placebo group were identified. The rates of REs I said

before tend to be less frequent with runny nose and congestion occurring in about 42 percent of subjects and coughs in about 24 percent, and the rates of REs were similar in subjects who had received one dose or two doses in year one.

This shows the results for the AV009, the adult trial. This is the entire study cohort of 18 to 64 years of age. Again, you can see the rate of at least one RE event was 70.9 percent for FluMist and 61.9 percent for placebo subjects. There were significant differences noted for runny nose and congestion and sore throat.

The rate of fever over 101 was very uncommon, occurring in less than .6 percent of both groups.

To summarize, between FluMist and placebo groups, significant differences were observed for runny nose and low grade fever for children and runny nose and sore throat for adults. REs occurred commonly in both groups, more than 60 percent in children and adults. We have no solicited RE data for seven to 17 year old subjects. There are no apparent differences in RE rates presented by the sponsor this morning by age group for subjects less than 50 or those 50 to 64 years of

age.

Most of the safety data available were generated in healthy subjects.

I'd now like to review additional concerns from VRBPAC of 2001. First we'll start with pneumonia. There was much concern at VRBPAC for possible increase in pneumonia after receipt of FluMist in AV006, year one. However, at that time not all studies were finalized and submitted for review.

Upon assessment across all 20 trials now finalized in the database, no increase in pneumonia, bronchitis or bronchiolitis events have been identified.

This gives those to you as data. In AV006, the relative risk at that time you saw in VRBPAC last year was 3.48 with wide confidence intervals. In 09, in 12 to 59 months, no significant increase nor for the 60 to 107 months, no significant increase, nor for the older age group of children.

We also discussed abdominal pain last year. There had been an increase in relative risk for abdominal pain observed in 06 in year one after dose one. This was a solicited event post

vaccination in that study, and the relative risk was 2.69, with a confidence interval or lower bound above one.

In the updated assessment across 20 trials we still observed the increase in 06, but there's a decrease in the relative risk in subjects less than nine years in 019, but remember these are medically attended events, not solicited events.

There's also a decrease in subjects 18 to 64 years observed in 09. Again, no intussusception, intestinal obstruction or mesenteric adenitis were reported.

For rare events potentially related to influenza in the review across all 20 studies, there were no reported cases of encephalitis, encephalopathy, Guillain-Barre, or Reye's Syndrome. There was no significant increase for central nervous system events, including seizures following the receipt of FluMist identified.

Additional concerns included concurrent immunization data. No data for efficacy or safety with concomitant immunizations in any age group are available. For the use of FluMist for five to 64 years of age, the possible concurrent vaccinations for the four to six year old age group include DTAP,

MMR, and inactivated polio vaccine for its possible use with pneumococcal vaccine.

Additional concerns included the need for annual revaccination data. At this time we have no data for revaccination of adults. For older children and adolescents from study AV012, there are 1,054 subjects who were immunized in both years one and two from whom data are available, and 459 of these were from the ten to 18 year old age group.

Those 459 had similar MAARI results and SAE results as presented for the entire study cohort. For young children under nine years of age, AV006 has year two and year three data -- at that time it was study 015 -- for safety and for efficacy.

As I reported earlier, there was no increase in reactogenicity events identified in repeat vaccinees, and there was demonstrable efficacy in year two. Year two included 1,358 subjects, and of those, 375 were over 60 months of age.

In previous VRBPACs, not just 2001, there have been discussions about annual release of influenza vaccine. Clinical testing for the new strains for code adapted influence of vaccine has

been performed by the sponsor. As you recall, the master seed virus is a 6:2 reassortant, which contains six genes from the attenuated master donor virus and two genes, the hemagglutinin and NA, of the wild type strain, and these are formulated annually.

The goal of this study was to test attenuation of newer reassortant strains in humans before incorporation to the trivalent preparation. The primary objective was to assess the safety of the new strain as demonstrated by similar rates of fever, defined as oral temperature above 101, in adults, CAIV, and placebo recipients from day zero to seven. This was based upon the fever rates observed in adults in 009.

For 2002 master virus seed vaccine contained ten to the seventh TCID50s for B Hong Kong in normal allantoic fluid. Plans, healthy adults randomized four to one with safety monitoring from day zero to seven, day zero to 14, and SAEs from day zero to 28 with a six month follow-up included.

Reactogenicity events were predefined as listed earlier. The study provided approximately 98 percent power to rule out a five percent absolute increase in fever, assuming a rate of fever of less

than one percent in the control group and that the true difference between the groups was zero.

A total of 330 adults were enrolled. Two hundred and sixty-four received the col adapted vaccine, and 66 received placebo. We have the initial safety phase data from days zero to seven. For the rate of fever above 101, there was one cold adapted recipient and no placebo subjects. The confidence interval around this was minus 4.9 to 2.3.

Thus, the study met its primary endpoint of less than five percent different. Also, there was less than or equal to five percent difference for runny nose and sore throat, which had been statistically significant different in AV009.

Additionally, this study demonstrated the feasibility of performing annual testing.

I will briefly review studies submitted in support of efficacy. This will be abbreviated as you heard much of it this morning.

First, 06 was the pediatric efficacy trial, U.S., multi-centered two year, prospective, double blind, randomized FluMist to placebo in a two to one ratio in healthy 15 to 71 month old children. It was initiated in the 1996-97 flu season with one

does in the two dose regimen, with two doses given 60 plus or minus 14 days apart, both being evaluated.

The primary endpoint was the first episode of culture confirmed influenza any time, on the day of, or after receipt of the second dose of vaccine.

There were several additional secondary endpoints which will not be discussed this morning.

At the time there was no H1N1 circulating in year one or year two, and thus, we do not have field efficacy data for this strain. You saw these data this morning, but just as a reminder, there was H3N2 and B analysis performed for efficacy against any strain, the number of culture positives. You can see for those who received two doses it was 93.4 percent with tight confidence intervals. Those enrolled in one dose was 88, eight percent with a little wider confidence intervals reflecting the small size, and for all randomized participants, the efficacy was 92.6 percent.

Efficacy by age group was also performed, and you can see for each group of interest over 60 months of age against any strain, the efficacy estimate was 90.6 with those confidence

intervals.

In year two, as I mentioned, 1,358 subjects returned. They received one dose of the same study vaccine that they had received in year one, i.e., they were not rerandomized.

The circulating strain that year, H3N2 was A/Sydney, and it was a variant from the vaccine strain of A/Wuhan. So against all community acquired influenza, there was 87.1 percent efficacy. Against A/Sydney, a variant, there was 85.9 percent efficacy with confidence intervals of 78 and 91.9.

An evaluation of efficacy by age group, again, for subjects over 60 months of age -- and remember they're now a year older -- efficacy against any influenza was 86.9.

Because there was no circulating H1N1, the sponsor performed a challenge study with a subset of subjects from 006. The goal was to compare viral shedding of vaccine strain, cold adapted, monovalent, A/H1N1 in previous FluMist recipients compared to previous placebo recipients.

A total of about 222 subjects, or 20 per site, were challenged with A/Shenzhen, H1N1, five to eight months after their year two vaccination. The challenge vaccine was the same lives as the H1N1

used in the year two vaccine.

After challenge, viral shedding was assessed on days one through four. The results showed 82.9 percent protection against shedding of the vaccine strain.

In the adult effectiveness trial, healthy working adults 18 to 64 years of age were randomized two to one to receive one dose of FluMist or placebo. The primary effectiveness objective was to show a smaller proportion of FluMist compared to placebo recipients had any febrile illness, AFI, during influenza outbreaks.

There were several additional secondary endpoints and illness evaluations, including severe febrile illness, SFI, febrile URI, FURI, CDC influenza-like illness, which is defined as fever plus cough or sore throat on the same or on consecutive days.

Additionally, comparisons of effectiveness for subjects under 40 and over 40 was defined prospectively, and a comparison of effectiveness for subjects under 50 and over 50 was performed in a post hoc analysis.

This slide shows the effectiveness against illness during influenza outbreaks for the

entire study cohort, looking at percent reduction, FluMist compared to placebo. For AFI it was not statistically significantly reduced. For SFI, FURI, and CDC ILI, all three illness categories did have significant reductions as you can see for the FluMist recipients.

The rates of AFI associated events in the total study cohort are shown on this slide. The days of over-the-counter medication use, days of antibiotic use had significant reductions. Days of health care provider visits and missed work days for AFI were reduced, though not statistically significantly.

The number of subjects enrolled by age group are shown on this slide. As you can see, for the 50 to 59 and 60 to 65 year olds, they were a smaller percentage of the overall study enrollment. In the pre-specified analysis in over 40 and under 40, percent reduction for illness categories is shown in this slide. It's 9.3 and for under 11.2 for over 40, and the differences with statistical significance are shown by asterisk for FluMist compared to placebo. There's no pattern. There was a decrease under 40 for SFI and for CDC ILI, but for those over 40, it's seen for FURI and CDC ILI.

In looking at subjects under 50 and over 50, again, asterisk shows significant decrease for FluMist compared to placebo subjects, and for those under 50 there was significant decrease for SFI, FURI and CDC ILI. No significant decrease in any of the illness categories were observed for subjects 50 to 64 years of age in this post hoc analysis in a small number of subjects.

For AFI, SFI, FURI, and CDC ILI, though there were no decreases in the occurrence of those illnesses, subjects 50 to 64 years of age compared to subjects under 50 did have greater reductions in illness associated events of missed work days, antibiotic use, and health care provider visits.

Additionally, a study of wild type influenza challenge was performed in adults. The objective was to assess the efficacy post challenge with wild type influenza against laboratory documented influenza illness in adult subjects. this is FluMist compared to placebo and FluMist compared to TIV, and TIV compared to placebo.

Laboratory documented illness included symptoms of influenza with identified shedding of wild type influenza and/or serologic response defined as greater than or equal to a fourfold rise

in hemagglutinating antibodies to the challenge virus.

Because there was a small number of subjects evaluated, with about 30 in each group, the laboratory documented illness for all strains combined showed efficacy of FluMist against the challenge of 85 percent and for TIV of 71 percent. These were statistically significant.

However, the study was not powered to assess efficacy against individual strains.

Efficacy conclusions. Efficacy against culture confirmed influenza illness was demonstrated after one or two doses in healthy children 15 to 72 months of age in year one and after revaccination in year two.

Efficacy was demonstrated for children in the subgroup of 60 months to 72 months in AV006. These are the only efficacy data available for children 16 months to 17 years of age. No field efficacy data for H1N1 are available.

Effectiveness conclusions. Effectiveness was not demonstrated in healthy working adults against the primary endpoint of AFI. It was observed against SFI, FURI, and CDC ILI in a post hoc analysis of the CDC criteria.

For the post hoc analysis of subjects greater than 50 years of age, there were no significant decreases in AFI, SFI, FURI or CDC ILI. Efficacy against culture confirmed influenza was not assessed in adults.

For safety conclusions, a total of 14,154 individuals, 60 months to 64 years of age have been vaccinated with FluMist. There are few subjects in the database over the age of 50 years. An increased risk of asthma events was observed in study AV019 in 12 to 59 month old subjects, but was not seen in subjects over 60 months of age.

No significant increased risk for pneumonia events was identified. Overall SAEs were recorded in less than one percent of the subjects.

With this review I'd like to acknowledge the great help of the clinical review team, Dr. Douglas Pratt, Dr. Antonio Geber, and Dr. Wasima Rida, our statistical reviewers. Our BLA committee chairperson is Dr. Roland Levandowski.

I now present for the committee the questions or would you like to ask me questions first?

CHAIRMAN DAUM: I think we'd like to ask you questions first and maybe begin --

DR. MINK: It was worth a try.

CHAIRMAN DAUM: We're awash in data here and probably need some clarification, and we can review these questions before we start the afternoon's discussion.

DR. MINK: Okay.

CHAIRMAN DAUM: So let's go to the committee for clarification questions at this point. Dr. Edwards, Decker, and Stephens.

DR. EDWARDS: I have two questions. The first is in assessing the reactive airway asthma data, it's interesting that there does not appear to be a temporal clustering of those, and if you look at the time between zero and 14 days, there did not appear to be more disease than if you extend it, which may be a function of a healthy patient effect.

But I wondered what your thoughts were about lack of temporal clustering. It seems that the biologic basis of reactive airway disease would have some temporal relationship to the administration of vaccine. So that was the first question I had.

DR. MINK: I don't have data to give you an easy answer. The temporal clustering was performed really primarily as post hoc, although

there was some plans for it the subject in AV019, to look at temporal clustering for events. So most of the data for temporal clustering are from AV019.

It's my understanding though with some respiratory viruses, such as RSV, that some of the reactive airway effects are long seen after natural infection and that they aren't necessarily temporally clustered.

DR. EDWARDS: But RSV and flu are different viruses. So okay.

The second question that I'm a bit confused about is the age 50 years to 64 year data. The ACIP has made recommendations in years with plenty of vaccine that that is a group at high risk or higher risk for influenza, and you just showed us some data from the effectiveness study that would suggest that perhaps the age 50 to 64 age group does not have as much effectiveness as in the younger group.

But then in a subsequent slide, you said the effectiveness looks good in that. So I'm a little confused in that. Could you please clarify that?

DR. MINK: Sure. The analysis in the subjects over 50 and under 50 was post hoc. The

study was designed, and I believe implemented before the CDC recommendations for the over 50 age group was in place. So in a post hoc analysis, we looked at the over 50/under 50.

The confusion is for the occurrence of the illness categories, AFI, SFI, FURI. There was no decrease in the over 50 group for any of those illness categories.

The next slide shows that for the illness associated events, such as health care provider visits, antibiotics, those events, there seemed to be a decrease in the 50 to 64 years even though there was no decrease in the occurrence of illnesses.

Does that clarify for you?

CHAIRMAN DAUM: Thank you.

I have Drs. Decker, Stephens, Faggett, Diaz, and Myers.

Dr. Decker, please.

DR. DECKER: Kathy asked the questions I had about efficacy. I've still got some questions about the safety data.

The occurrence of asthma in the younger children, which although there's a question about the cluster, it seemed as I saw the data you

presented and in the pre-read, it looked as though this was popping up in multiple looks at the data, making it more convincing it might be real.

But it also looked to me as though it was only really being seen after the first dose and wasn't an issue in the second dose. Did I see that correctly?

DR. MINK: According to the data from AV019, the statistically significant increase was only after dose one. It was not significantly increased after dose two in the 12 to 59 months or the older children either.

DR. DECKER: Which led to a question in my mind. It made me wonder if prior experience with influenza virus perhaps through inactivated vaccine would convert these first exposed children to second exposed children. Are there any data on that?

Has there been any look at what happens if you give the FluMist product to people who previously received, and particularly to these young children who have previously received the inactivated product?

DR. MINK: I don't have data for a subset of subjects who receive flu inactivated vaccine and then subsequently received FluMist.

However, I know some subjects in the database, you know, going back in their histories had received flu. I don't have a large enough or even a comprehensive evaluation to tell you what the reactogenicity profiles of those subjects are.

CHAIRMAN DAUM: Dr. Stephens, please.

DR. STEPHENS: My questions are somewhat similar and deal largely with the over 50 group, which I think is problematic for at least some of us. I had a similar question to Dr. Decker, and I think you answered it in terms of prior influenza inactivated vaccine in that particular cohort. You really don't have that information; is that right?

DR. MINK: I don't have the data separated out by who received flu vaccine previously.

DR. STEPHENS: As I understand this group, we're talking about an n number of 511; is that correct or close to?

DR. MINK: For FluMist.

DR. STEPHENS: For FluMist in the over 50 age group.

DR. MINK: In AV009, right.

DR. STEPHENS: In 09, which is the large part of the data set for this particular -- so we're

talking about relatively small numbers in this particular category.

DR. MINK: Right.

DR. STEPHENS: There was a VA study mentioned earlier by the sponsor. It looked like that study was withdrawn from the license application as well as two other studies. Can you comment on that?

I mean, that would be more data that I think some of us would be looking for in this particular group.

DR. MINK: Those subjects weren't in the age cohort being requested, and they were not healthy subjects. They had at least one risk factor for needing inactivated vaccine. So they're not included in the database in healthy individuals five years to 64 years of age.

CHAIRMAN DAUM: Thank you.

Dr. Faggett, please.

DR. FAGGETT: Concerning the Texas HMO trial, I'd like a couple of questions. Number one, what population was studied there, and could you let me know if the Medicaid population was included in that study? That's the first part of the question.

DR. MINK: Yes. It was predominantly

subjects from Temple Belt in Texas, with most of them being seen at Scott & White Clinic HMO. About 80 percent of the subjects had Scott & White coverage, but many of the other 20 percent were Medicaid.

The ethnic diversity of the study was representative of Texas.

DR. FAGGETT: And the purpose of the study was to look at herd immunity, and the safety information was secondary to that?

DR. MINK: In the original design.

DR. FAGGETT: Okay. So I'm just not clear on what conclusions. The study raises more questions than it answered. It would appear as if the implication there is increased risk of asthma and wheezing in young children from that study.

Is there any other conclusion I could draw from that?

DR. MINK: I have the data presented that there was no increase in MAARI events in year one, but there was an increase in year two. The year one started in August, and everybody finished before flu season started. Year two started about a month later, and not all of the subjects completed their follow-up before flu started. So there's a

lot of complicating factors in that study.

DR. FAGGETT: So it's really difficult to draw a good conclusion from it.

DR. MINK: The conclusion that I provided for you is that 9,500 or so doses were given, and the rate of SAEs was comparable to the randomized double blind trial of about .02 percent, and that -- there was one more -- and that there was no rare events associated with influenza identified in that trial.

DR. FAGGETT: Yes.

CHAIRMAN DAUM: Thank you.

Dr. Diaz.

DR. DIAZ: Just two questions. In reviewing the duration of shedding for the different influenza strains, you made a comment about the H1N1 data, the range being out to 21 days, and yet that was the last date that culture shedding data was obtained.

DR. MINK: Right.

DR. DIAZ: Are we to assume that with the H3N2 and the B strains since the range is three to 17 and one and 15 that there's actually endpoint data at 21 days to show that there was no shedding at that time?

DR. MINK: Yes. Twenty-one days was the last day cultures were obtained.

DR. DIAZ: Okay. Thank you.

And then perhaps my colleagues that have raised questions about the concern about the reactogenicity associated with the first dose disappearing with the second dose and questions about perhaps data about prior immunization with the current influenza vaccines, the killed vaccines, I just wanted them perhaps to clarify for me the interest in having that data.

These seem to be very different vaccines obviously, and presumably individuals especially in the older age groups, if they hadn't had experience with prior immunization, would certainly have had experience with prior influenza. So is it the egg product or what is the interest in the prior immunization with the killed vaccine?

DR. DECKER: Well, I'll answer my question. My thought was that if it's, in fact, the infection with the vaccine virus in the FluMist that's triggering in some small proportion of children these reactive airway events, that in these kids who were getting a two stage immunization, two doses a month apart, if you first immunize them with

the killed vaccine, which should not trigger the airway event, you may induce enough immunity that they're protected from the reactive airway disease when they get the dose of the live flu. So you may get the best of both worlds and avoid this possible reactive airway disease pathway.

So it's a speculative question, but there are some other vaccine situations where we've seen similar things happen.

CHAIRMAN DAUM: I really want to interject at this point and return to the presentation from the FDA about this FluMist vaccine. This certainly is some interesting speculation that if time permits we could explore this afternoon, but we're not really talking about a sequential schedule at this point. I'd like to focus on this presentation right now.

Pam, were you done or did you have a follow-up?

DR. DIAZ: I had a follow-up, but we can do it over lunch and then see if we need to bring it up.

CHAIRMAN DAUM: Perfect. Thank you.

Dr. Myers and then Dr. Eickhoff, Dr. Edwards.

DR. MYERS: I think Dr. Faggett addressed part of the issue. There are a lot of issues with the 012 study, but to get at the issue of timing and frequency of asthma and URI, whether this is a normal rate of illness in the normal population and so on, as I understand the analyses that were done, we looked at comparison periods before and remote to the immunization, and the only data we've seen is relative risk and confidence intervals. Could we actually see illness rates in the comparison periods? Would that be of value, or are you seeing so many problems with the study that it wouldn't be?

DR. MINK: There are a lot of comparisons, and there are several limitations to the data. So I think it would be with caution for interpreting the actual event rates.

CHAIRMAN DAUM: Thank you very much.

Dr. Eickhoff, please.

DR. EICKHOFF: A comment and a question. My institutional memory of this committee is probably as good as anybody's and is really better than most, but it is difficult to remember any occasion in which the sponsor's analysis of the data and the FDA analysis of the data had such a high

level of concurrence. So that tells us something.

My question is, Mr. Chairman, not a question of the FDA data, but a general question which I'll be happy to save for this afternoon.

CHAIRMAN DAUM: I would prefer that, Dr. Eickhoff, if that's okay with you. I think we really want to focus on debriefing all of the aspects of this that we need to hear about, but please don't throw your comment away and please return to it.

I have Dr. Edwards, Gellin and Goldberg.

DR. EDWARDS: I want to just make a comment that I think some studies that we did almost two decades ago now that were funded by NIH that looked at John Maassab's product, not the FluMist product, and subsequent studies have shown very clearly that the more experience that you have had with a flu strain, either with inactivated vaccine or with subsequent infections, it appears that the titer of cold adapted virus that would grow in people that have had less immunity is different than in people who had more immunity.

So I think it is relevant and makes wonderful biologic sense that the first dose, if it was going to be more reactive, would be because the

titer of virus would be greater than the second where you would have some preexisting immunity and the titer would be less.

And I think that's what's being shown also in the reactogenicity data in the young children as opposed to the older people. So I think it is biologically relevant, and I think it sort of addresses Pam's question, but would also make it, I think, more comforting that if you had been previously primed with an activated vaccine and then followed cold adapted; that I would anticipate there would be less of an issue with reactogenicity than with more.

CHAIRMAN DAUM: Thank you very much.

Dr. Gellin.

DR. GELLIN: Let me just follow on to Kathy's question and ask a different one.

Was there a correlation between reactogenicity and shedding?

DR. MINK: Actually that question was asked this morning, and as I recall Dr. Connor said he didn't have data directly assessing that, with the primary reason being that most of the concerning adverse events were identified after the studies were completed.

Shedding was only routinely performed in four of the trials. AV002 was one of the very early trials, and AV011, which was the challenge study, and then the Wyeth transmission study.

I guess it's still possible to look at reactogenicity data compared to the shedding for those subjects, but that has not yet been done.

DR. GELLIN: And then just a point of clarification, in the many slides you showed us on the SAEs your conclusion was no pattern seen among the various events. Would you elaborate another half sentence on that?

DR. MINK: Yes. Actually in your briefing document, I provided a line listing of all the SAEs for year one and year two in AV019, a total of what is it, 24 events? And there is really no pattern.

Some of them were accidents. Some of them were, you know, surgery for a toe injury. There's a collection.

CHAIRMAN DAUM: Dr. Goldberg, please, and then Dr. Snider.

DR. GOLDBERG: Can you just clarify for me? You said that 20 vaccine strains were isolated from ill FluMist subjects and that there was no

reassortment in those 20 strains. Does that make you feel comfortable that we don't have to worry about this?

DR. MINK: Dr. Levandowski, would you like to comment about the reassortment from the 20 ill? Is he still here?

DR. GOLDBERG: I mean, I can clarify my question a little more.

DR. LEVANDOWSKI: I'm Roland Levandowski. I'm with the Center for Biologics also.

I don't know that there's much of a comment that we can make on that. There's a small number of strains. It's the information that's available to us, and to the extent that that says that reassorting doesn't occur, I think that's the only conclusion we can draw from that small sample that we see. It's reassuring, but we can't necessarily predict that some event couldn't occur in the future.

DR. GOLDBERG: My concern is that observing nothing in 20 could still be compatible with a fairly substantial underlying rate, and I was wondering if you had any further data or from other models or animal work or the sponsor perhaps.

DR. LEVANDOWSKI: I think that was addressed by the sponsor also this morning in talking about seeing reassorting occurring between the cold adapted strains within the vaccine recipients. There is some evidence to suggest that.

And we know from natural occurring influenza, one example this past year, the appearance of H1N2 influenza viruses is a natural reassorting event between the HAN1 strains that have been circulating and the H3N2 strains that have been circulating.

So reassorting events would be expected to occur, but there's no evidence that we have that that's occurred with the cold adapted strain.

DR. GOLDBERG: Thank you.

CHAIRMAN DAUM: Dixie.

DR. SNIDER: Yes. Two comments. One, my recollection, and Nancy can correct me, Roland, if I'm wrong, but the H1N1 issue, of course -- I mean, the statement is true that there's no field efficacy data for an H1N1, but the fact is there hasn't been much H1N1 circulating.

So to try to get that data we don't know how long we'd have to wait, and so I think, you know, this year maybe, maybe two years, who know

when? So, you know, the challenge data may be the best surrogate.

The question I had is, or maybe it's a reflection, is that, you know, I certainly think the comments that have been made about the use of inactivated vaccine in advance of using FluMist may have some merits, but there's also the issue that is not addressed in the database we have unfortunately, at least not that I'm aware of, but I have a question about it, and that is natural infection causes reactogenicity, runny noses, and I would presume precipitates asthma attacks, maybe even more severe.

So one of the potential things that could be happening here with the vaccine strain is that you're eliciting mild flu symptoms with an attenuated strain, and hoping that you're trading off those milder episodes of reactogenicity and milder episodes of asthma for more severe episodes.

I realize that may be hypothetical, but the question for the sponsor and FDA is is there any data in any of these databases that might support the hypothetical statement I just made.

CHAIRMAN DAUM: Do you want to answer that briefly? It's sort of an afternoon question.

DR. MINK: Okay. Then I'll see --

(Laughter.)

DR. SNIDER: Okay. I yield, Mr. Chair.

CHAIRMAN DAUM: Well, perhaps we can save it.

DR. SNIDER: I can eat, you know, now.

CHAIRMAN DAUM: No, we've got to address this, and there's at least three committee members that would like to hear a discussion about it, but would you be upset if we deferred it until after we came back?

DR. MINK: I wouldn't.

(Laughter.)

CHAIRMAN DAUM: My goal here is to try to get us to lunch at 12:15, and Dr. Katz is waiting to speak. So we'll hear from him, and then I think we'll hear from Ms. Fisher, and then we'll take a lunch break.

DR. KATZ: I guess mine is more a generic question. We've heard about from both the FDA and the sponsor about reactogenicity, effectiveness, efficacy. I've heard nothing about antibody data, and I'm wondering have those disappeared from our radar screen. What is their relevance?

Basically, you know, if we're looking at some of the old experience, you know, and initial exposure to given antigens or epitopes, and then second, with new strains of influenza coming along presumably in the cold adapted vaccine or any others, you may reinforce the antibody response of your primary, but your new ones may be less robust, which is the current adjective people seem to use.

Do we have any antibody data or do we consider them important anymore?

DR. MINK: We do have antibody data. Those were presented last year, and we elected not to revisit the serologic profiles this year. The primary reason we elected not to revisit serology this year is that no correlate has been identified following FluMist. Actually probably, depending on who you ask in the room after an activated vaccine with without a clear correlate for serology and even more of a quagmire is perhaps the local immunity, nasal immunity, that we chose not to revisit the issue this year.

CHAIRMAN DAUM: Ms. Fisher.

MS. FISHER: The subject with transmitted vaccine virus had flu illness symptoms. How confident are you from this data that the

transmission rate would only be about five percent if the vaccine was used on a widespread basis.

DR. MINK: The data I presented are the only data that I have estimating the rate of transmission or the probability of transmission, and in our conclusion we felt most comfortable saying that transmission does occur, but at this time we can only estimate a crude rate.

CHAIRMAN DAUM: I feel confident we will return to the issue of transmission this afternoon.

We're going to take a lunch break of 60 minutes duration. There are two choices within the hotel: Allie's American Grille or the Lobby Lounge. Good luck, everybody, getting served.

We will convene at 1:15 sharp with the open public hearing and go right on to the afternoon's discussion.

(Whereupon, at 12:18 p.m., the meeting was recessed for lunch, to reconvene at 1:23 p.m., the same day.)

AFTERNOON SESSION

(1:23 p.m.)

CHAIRMAN DAUM: Can everybody please take the seats and call the meeting to order for this afternoon?

Is Dr. Sachs in the room?

While we're waiting for Dr. Sachs to come I'd like to correct for the record an issue that came up this morning. During Dr. Young's presentation, he kindly attributed to me the benefits of having done some studies on influenza virus as it relates to FluMist. However, wrong guy. I'm not the person who did those studies, have never done studies with influenza virus or FluMist or else I would not be sitting here today.

Those studies were done by Dr. Maassab, and the record should show M-a-a-s-s-a-b is the person who performed those studies.

Thank you very much for lengthening my CV, but I can't accept that at this moment. We now -- or any other moment. It's my last meeting.

We're now going to convene the afternoon's business and begin with the open public hearing. I'll turn the floor over to Dr. Sachs for that portion of the meeting.

DR. SACHS: This is the point where anyone from the public is welcome to speak briefly. No one has requested time from me earlier, but you're more than welcome now, you know, to come up and announce yourself.

If there's no one who wishes to speak publicly, I'm going to close the open public hearing and resume our meeting.

Thank you.

CHAIRMAN DAUM: Okay. What I'd like to do is our style in the committee is to allow the committee to explore whatever issues initially interest them that arose from this morning's presentations.

I think in order to understand what field we're playing on it might be good to ask Dr. Mink if she's here to put the questions up briefly so that we can just see them, and then we'll have committee members as they wish raising issues of their pleasure.

DR. MINK: Question one for the committee is for safety and for a vote.

One (a), are the data adequate to support safety of FluMist for individuals five to 17 years of age, 18 to 49 years of age, 50 to 64 years

of age?

Please consider data related to respiratory events, such as asthma and URI, shedding and transmission of the vaccine strains following receipt of FluMist, and annual revaccination data. If the data are not adequate for specific age groups or there are other safety concerns, please discuss what additional should be requested.

Question two, efficacy for a vote. Are the data adequate to support efficacy of FluMist in individuals five to 17 years of age, 18 to 49 years of age, 50 to 64 years of age?

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

Discussion point number three. Clinical studies for release of new strains. Please comment on the design and endpoints for the clinical studies performed in adults for the release of new strains.

Discussion point four. For additional studies, if the data are adequate to support safety and efficacy, please discuss what additional information, if any, should be requested from post marketing studies.

That's all.

CHAIRMAN DAUM: Thank you very much, Chris.

So the first two questions are going to need a committee vote. The third and fourth questions are discussion questions, and so we can leave the questions now and digress really to issues that committee members would like to explore based on this morning.

So, Dr. Stephens, would you start us off, please? Then Dr. Cox.

DR. STEPHENS: Could we clarify that the questions relate to healthy individuals? Is that correct? So the word "healthy" is a part of it?

DR. MINK: The word "healthy" should be in the slides, yes.

CHAIRMAN DAUM: That's an important clarification, David. Thank you.

Dr. Cox.

DR. COX: Yes. With regard to the question about transmissibility, I'm wondering why investigators were not able to obtain the original clinical specimens from those individuals who were believed to shed influenza viruses and then just PCR and sequence the viral nucleic acid to find out if those were actually wild type or cold adapted

viruses.

CHAIRMAN DAUM: Okay. For this question we will turn to the sponsor. Do you care to respond to that?

Please identify yourself. Thank you.

DR. COELINGH: Dr. Coelingh from Medimmune.

The nasal swabs, Nancy, that were taken, I'll just go through how the study was done. The nasal swab specimens were taken in Finland, and they were inoculated onto MDCK cell cultures in duplicate. One of those cultures was used for immunostaining with monoclonal antibodies to identify whether there was an influenza virus present in that specimen.

The other specimen was frozen and sent to Medimmune where we did phenotypic analysis, genotype, et cetera, and subtype analysis to identify what type of strain was in the specimen.

Okay. Those specimens were frozen and sent to Medimmune for further analysis. Some of those viruses we could not identify a virus in that isolate.

And to go on to the rest of your question, in the ones that we couldn't identify any

virus to subtype, we went back and inoculated those into eggs, and we blind passaged in both MDCK cells and Rhesus monkey kidney cells and had HAs on those and also tried to RTPCR virus using primers specific for the M and the MP genes, and we were unsuccessful at doing that even though all of the controls worked appropriately.

CHAIRMAN DAUM: Thank you very much.

Dr. Eickhoff, please.

DR. EICKHOFF: Let me readdress the question that was on my mind earlier this morning and I think on Dixie Snider's mind as well, and that relates to the general area of wild type influenza and asthma in healthy children in the one to five year old age group.

I know that Ken McIntosh 25 years ago did some studies of wild type influenza in children at National Jewish Hospital, and so these were children with preexisting airways, disease, and I don't remember the exact nature of it, but not surprisingly influenza exacerbated their reactive airways disease at least as measured by pulmonary function tests.

But what do we know about wild type influenza and asthma related events in healthy

children in that age range?

Any pediatrician on the panel may respond to that.

CHAIRMAN DAUM: Kathy, would you like to start that response?

DR. EDWARDS: I think the data that I can recall most quickly are data that were generated from a database, the TennCare database, which although it doesn't fund doctors well at all, it does create a database that you can query in terms of events.

And in some data that was published in the Journal of Pediatrics or Pediatrics the year before last, Kathy Neuzil looked very carefully at the TennCare database and showed that the numbers of visits to doctors' offices and individuals that had previously been given either bronchodilators or had an ICD-9 code of asthma was significantly increased during the flu season when it was compared with other individuals.

So obviously that's retrospective data, but I think showed quite clearly that children with asthma during flu season will have more encounters, more wheezing episodes, more illnesses than those who do not.

CHAIRMAN DAUM: Thank you.

Other committee members? Dr. Snider.

DR. SNIDER: Well, I just would add as an allergist-immunologist who tries to keep up with the literature, I think there is, just to build on what Kathy said, an increasing appreciation of the role of the number of respiratory viruses in triggering episodes of asthma. So I think the idea that natural influenza infection would be responsible for triggering episodes of asthma in children who are so predisposed is not only hypothetically and biologically plausible, but has, indeed, started to gain scientific evidence base.

CHAIRMAN DAUM: I'd like to throw out a couple of questions just for comment. One of them was inspired by a comment that Dr. Katz made this morning, and that is that supposing there is transmission, the first question is is that a good thing or a thing that we should be concerned about.

The model of OPV was mentioned this morning as one kind of vaccine that did have transmission in one part of it's life in this country. That was a helpful thing in terms of preventing polio. Is that a good thing?

And then the second thing is

transmission to whom exactly, and what do we need to know, if anything, more than we do now about what kinds of recipients, hosts the viruses might be transmitted to? And where are we in terms of our understanding about that?

Those are two questions that I would love -- I don't know the answers. If people would comment about them. Does anyone want to speak directly to them? Dr. Overturf?

Dr. Markovitz, I've got you in line when we change topics, b ut I'd like to explore this just a little bit first.

DR. OVERTURF: Actually I think it's a major issue, and I agree with Dr. Myers' comment this morning that it seems to me that when you move the shifting of the vaccine program, and we actually have shifted with this vaccine a concern using large amounts of vaccine in otherwise normal, healthy individuals, and before the issue had been primarily giving to children who were at higher risk and elderly adults.

But when you do it in this population, I would like to have more information about how the vaccine virus -- what it will do in a large, open population in terms of transmissibility to others

and whether that transmissibility actually increases the hazard to populations that we really haven't addressed, like asthmatics, patients with COPD, patients who are smokers, and a lot of other issues.

And I don't think that the data that we have now really addresses those issues because it's too small. But I agree that moving it from a population of high risk, moving it from a situation where you're protecting high risk populations to healthy populations, the issue is are we going to actually incur more problems than we actually solve in that setting.

I think that needs to be addressed, the safety of the vaccine. When I was going back over the historical data that was provided by the sponsors in terms of persistence of virus, there was very little data particularly in the population over 50, again, about how long the virus is there and if it's transmitted in that population, and I think that's an important question.

CHAIRMAN DAUM: Thank you.

Could we keep the discussion on this issue for a few minutes?

Dixie and then Pam.

DR. SNIDER: Well, just to build on what

Gary just said, I think one other thing to throw in that mix is whether those other populations have received inactivated vaccine and how that might impact on whether they have any adverse outcomes as a result of this transmission is, again, something we don't know, but is important to know because there may be a way if there is significant transmission, and there were these adverse events that would occur in individuals, it's conceivable that they could be attenuated if the high risk individuals received inactivated vaccine before they were exposed to the attenuated vaccine.

CHAIRMAN DAUM: Dr. Diaz.

DR. DIAZ: Likewise that was the major reason for my question earlier about in household transmission, was the concern about potential high risk individuals within a household setting where a healthy individual in that household may actually be immunized with this vaccine virus.

And likewise I was not necessarily reassured, and perhaps the manufacturer can comment, if there were household transmission studies done with that particular interest in mind, i.e., transmission to high risk individuals.

And finally, the issue about shedding in

children out to 21 days, likewise if there's any data or should there be data about potential shedding in higher risk individuals who may shed a much longer period of time.

CHAIRMAN DAUM: Does the manufacturer wish to respond to the question of Dr. Diaz?

You can use either this mic or that mic, totally your choice. Easily solved.

DR. CONNOR: Let me for a moment try to just put into perspective some of our thinking about the transmission issues.

First of all, I think as we mentioned earlier this morning there are some data that look at transmission in the historical studies. Those were referred to earlier. There are a number of studies that have looked in various settings, including household contacts and husband-wife pairs, that have not been able to demonstrate transmission in that setting, although obviously those were smaller studies than these are.

DR. DIAZ: And not necessarily in a setting where that household partner is a high risk.

DR. CONNOR: Is a high risk patient, right, although there have been high risk patients studied in that population, including patients that

in normal populations of families, but not specifically targeted at the high risk populations.

The other sort of factors to think about are that there are a number of factors that are going to influence vaccine virus transmission obviously. They're going to be either the frequency of virus shedding; how many people in the population are actually shedding virus; the level and the duration of shedding; the susceptibility of the contacts as referenced to the prevalence of TIV in vaccination in which you've got seropositive contacts shedding for shorter periods of time and the intensity of the contact.

And if you then just think about the next issue, which is that the inoculum of the shed virus is obviously much less than the inoculum of the vaccine administration so that you're actually getting less virus in a transmission situation than you're getting in active vaccination, but there's a low probability of transmission. How you calculated the probability is quite low. Our estimates based on the Reed-Frost model would be that it would be approximately .006 or so.

We've also done some work with Ira Longini who has looked at the population modeling of

the FluMist transmission models, and using the transmission rates that are the 006 rates, if you calculate the reproductive number associated with this virus, it turns out to be well less than one.

So, in effect, mathematically it's implausible that the transmission of the vaccine virus would actually represent any more than some secondary transmission, but it wouldn't persist in the population is what those calculations tell us.

And there obviously then is a low rate of transmission in the older kids and in adults compared to the children in the day care settings that were studied.

I think for most of us -- George, the next slide for a second -- this just illustrates something that I've shown before, but maybe we can go to the next one first, which I think what we're talking about are what are the consequences of transmission. I mean, what are the problems if transmission actually occurs, and I think I've already addressed the first one, which is there's a risk to the population, and we should understand what that is in terms of the risk of transmission.

Ira Longini suggests to us that that is not possible to perpetuate the CAIV virus in the

population.

The other individual questions are what is the risk to individuals, and the individuals of interest are either an immunocompetent host so that the transmission occurs in the household or someplace else, to another person who is immunocompetent. A couple of things are going to happen, not the least of which is that that person is going to respond to the vaccine, and they're going to shut off virus shedding.

So at worst transmissions with immunocompromised hosts would be equivalent, although it would actually be less because the dose would be less, than giving that person FluMist.

The immunocompromised individuals, a setting in which what one thinks about, are first of all the virus is temperature sensitive. So presumably transmission to an immunocompromised host going to produce an upper respiratory tract infection, and that it would remain limited to the upper respiratory tract by and large, but prolonged shedding would probably happen. The immune response would not allow the virus to be shut off quite as readily in an immunocompromised host than in a immunocompetent host, and that would allow -- and

obviously there are antivirals that could be used to treat such situations.

And the other possibility, as folks were mentioning, is so what's the probability in an asthmatic. Again, if you think about the risk, it is at least equivalent or no worse than the data that we provided to you about FluMist.

So you may see some low frequency of wheezing and exacerbation and that is balanced against the benefit of the vaccine which prevention of wild type influenza in the first place.

And if you're interested, we have thought a bit about so what is the -- I don't know. For me medically, I sort of have to put that into some context. What's the actual risk that something would happen in the population?

If you think about that and just go on, this is the kind of way in which we've been thinking about it. The first is that you have to make certain assumptions in a simplistic kind of modeling approach, and the assumptions would be that the inoculum from the transmitted virus was equivalent to giving the virus. I mean, that's what we know is what would happen under those circumstances.

If you assume that the transmission rate

in the household setting or in the school setting, here we did it for thinking about an immunocompromised person in school; that the transmission rate would be what was in day care. That's the worst case scenario. It clearly would be better than that in other circumstances.

And if you estimate the number of immunocompromised hosts that are out there in the school age population in a six year or seven year school situation, the prevalence if you add up the cancer transplant, chronic steroids, HIV, congenital immunodeficiencies that would happen in that population would be about .0015 percent. The rate is about that.

If you assume that everybody was fully immunocompromised so they continued to shed virus and they were all in school, which is obviously an -- these are all very conservative kind of estimates -- the calculated risk of transmission based on the day care transmission rate would be something like .0000009. So the rate is low in those kind of settings that an individual would transmit to an immunocompromised host in the school system, and it's likely to be less than that because, in fact, the inoculum is not equivalent to the vaccine dose,

and there are other characteristics.

And you can go through those same kinds of exercises for asthmatics and look at excess risk associated with the population also, and just the next slide, George.

You go through the same sort of analyses, making certain assumptions, and if you assumed that the asthma wheezing risk was as bad or what it was in the patients that were less than 60 months and the history positive patients, you'd calculate a risk of excess asthma and wheezing that also would be quite low.

So I don't know if that helps. There obviously is a lot of assumptions built into that kind of thinking, but it gives some kind of context in which to think about sort of the medical circumstances in which those things would happen.

DR. YOUNG: Dr. Daum, can I make one more comment?

CHAIRMAN DAUM: Please. A succinct one.

DR. YOUNG: Okay. George, can you just put up that table?

I want to just clarify something for everybody because we talk about transmission is transmission and it's the same in everyone. We need

to look at some of the fundamental shedding infectivity data for different populations that we know about with CAIV.

Ed showed this slide early on. In children you see much higher levels of shedding when you infect them with CAIV. Their peak titers are two to three logs of virus, and their duration of shedding is four and a half to nine days.

Adults shed less. They shed far less virus. You can see this one to two to three logs lower, and the duration of shedding is only one or two days.

So when we're talking about adults who get immunized with this vaccine, they're making a lot less virus for a shorter period of time than day care kids are shedding where they're seronegative.

And then look at the infectivity when you do challenge studies with different strains of CAIV. You need two and a half to four and a half logs of CAIV to infect the child. You need five to six and a half logs to infect a human.

So if you just think about --

(Laughter.)

DR. YOUNG: Sorry. To infect an adult.

CHAIRMAN DAUM: There you go again.

DR. YOUNG: There I go again, Dr. Daum.

(Laughter.)

DR. YOUNG: These were studies Dr. Daum did -- only kidding, only kidding.

If you look at how much a child sheds, it's virtually impossible for them to infect an adult. If you look at how much an adult sheds, they can't infect a child or an adult with the amount of virus that's being shed. So the likelihood of transmission from adult to adult, adult to child, or child to adult is very low, very much lower, for sure than child to child where they're seronegative. They're making more virus. They're more infectable.

So don't think about transmission as the same from person to person, whoever get the vaccine. I think you need to remember that that's the case with this virus. It's different than wild type where you're getting more levels of shedding than you do with CAIV.

CHAIRMAN DAUM: Dr. Young, I think you had too much sleep last night.

(Laughter.)

CHAIRMAN DAUM: We're going to take one question from Dr. Steinhoff about -- oh, could you leave that on, whoever took it off? -- about this

very slide.

Dr. Steinhoff, this very slide.

DR. STEINHOFF: It's about the previous slide because I just wanted a clarification, and others may all understand this, but I don't quite understand how you use that probability number from the Reed-Frost calculations.

You quoted a number somewhere between .006 and .04 as a probability, and I'm gathering, but I don't know; perhaps you could explain. Is that the probability derived from the study in Finland of a single excreter infecting at least one other person in that setting? Is that what that is a probability of?

I'm not sure. I mean, what's the numerator and what's the denominator?

DR. KOHBERGER: Bob Kohberger from Wyeth.

That transmission probability is one to one, one infected, one susceptible. Yes, that's susceptible, becoming infected.

DR. STEINHOFF: That means then you'd have to multiply this by a variety of factors, how many shedders you have and how many susceptible you have, which then brings in all of the other factors

of how many people are immunized and how many are susceptible in actual contact; is that correct?

DR. KOHBERGER: That is true. If you have 100 infected and one susceptible, they're more likely to get infected than one to one.

DR. RIDA: Might I offer a suggestion?

Wasima Rida, Biostatistics at CBER.

The basic reproduction number is a product of that transmission probability times the expected number of contacts in an entirely susceptible population. That's the formal definition.

So to calculate the basic reproduction number, you would have to know what is the expected number of contacts a FluMist vaccinee would come into contact during their infectious period. So that's basically what a basic reproduction number is.

CHAIRMAN DAUM: Thank you.

I think that was a clarifying discussion.

Dr. Hamilton.

DR. MINK: Dr. Daum.

CHAIRMAN DAUM: Dr. Mink.

DR. MINK: Actually on the table, can

you show that again, please? That one.

Please can you tell us are those subject FluMist recipients or does this include all of the historical experience, NIH, et cetera, for -- okay. Thank you.

CHAIRMAN DAUM: All right. So we'll try to move on. This has been very helpful though. I think it has clarified some issues and some uncertainties perhaps.

Dr. Hamilton, you've been patient. Then Dr. Steinhoff and Katz.

DR. HAMILTON: Just one more question. When child is used, does it refer to everyone under 17? Is any data on this broken out between a five and five to 17?

CHAIRMAN DAUM: Would the sponsors care to respond to that?

DR. HAMILTON: When you use the word "child," what age groups are you referring to? Because we're asked to opine on one to five years and then five to 17 years.

CHAIRMAN DAUM: I don't think we're going to be asked to opine about one to five. Maybe we could see the table again that Dr. Hamilton is trying to explore here.

DR. HAMILTON: So children is one to 17, and we don't have data broken out for the five to 17 year olds, and that's what we're asked to opine on.

CHAIRMAN DAUM: Can you come to the microphone? Tell us who you are.

DR. MURPHY: My name is Brian Murphy.

CHAIRMAN DAUM: Any connection to FluMist, please?

DR. MURPHY: Excuse me. My name is Brian Murphy. I'm from NIAID.

We did these studies. The children here are young children generally, approximately six months to three years of age, who were chosen to be seronegative to the virus that was given. So they represent basically immunological versions.

So those HID50s are basically what you would see, the infectivity titrations of viruses in individuals who have no immunity to the virus. The adults are people who are age 16 to probably 40 or 50 at the time these studies were done.

There's one other point I just wanted to make. The question of household transmission that you had talked about. This virus has been given. The Influenza A virus has been given to two month old children, to very young infants, and was shown

to be safe in that age group.

Conversely, it has also been given to very old individuals, definitely greater than 65 years of age at ten to the seven in both cases, and it has been shown to be safe in those populations.

So even if it does transmit, if it transmits to individuals at the very ends of the spectrum of age, the virus should be safe in those rare cases of transmission if it occurs.

CHAIRMAN DAUM: Dr. Katz, we're staying on this transmission issue for now. Is your --

DR. KATZ: Yeah, I'd like to set this into an appropriate context. We're spending all of this time talking about transmission of an attenuated virus. We're not contrasting it with the transmission of wild virus. It's a matter of education, not of science, of how we use influenza vaccine. All of these household contacts, all of these high risk people by our current recommendation should have been immunized with trivalent inactivated vaccine.

So the issue becomes moot if we have program that work, if we educate health care people, if we educate the public.

So I think we're losing perspective in

focusing so on transmission of the attenuated virus. We're not even contrasting it with what happens with the wild virus if a child brings it into the home or if a day care person.

All of the routes of transmission we're talking about, we're trying to interrupt the transmission of wild virus. I don't think we're appropriate in placing such emphasis on the transmission of attenuated virus.

CHAIRMAN DAUM: Dr. Stephens and then Dr. Snider. We're staying on this subject till we're finished with committee interest, and then we'll move on.

DR. STEPHENS: It would at least seem to me on the surface that the 019 trial where you have this Kaiser database of families could be useful in assessing some of the questions at hand in that would it be -- and maybe it has not been done -- but it would be helpful to have looked at the family issues of asthma or other respiratory illnesses or other events occurring in families of the children with this database.

And my question is really to the sponsor, whether that was looked at at all to help address this particular transmission issue.

CHAIRMAN DAUM: Dr. Mendelman.

DR. MENDELMAN: Paul Mendelman, Medimmune Vaccines.

Specifically in the 019 trial it was not addressed. However, there was an intriguing analysis in the pivotal efficacy trial, AV006, Dr. Belshe, and in that trial, it provided indirect information about the lack of transmission, and what was done in that trial is that -- and Bob is here to either correct me or comment if needed -- because more than half of those children were in families that were vaccinated in that 1,602 child trial and allowed the opportunity to look at a sibling who got vaccine and a sibling who got placebo compared to singleton placebos.

And it turned out that the children in those families that had both a vaccinee and a placebo the attack rate in those placebo children for wild type flu during the flu season was the same. They had the same attack rate essentially. So they were not protected by the child, a sibling of theirs giving them transmitted vaccine virus and protection downstream.

It's indirect. It's intriguing, but it is information.

And, Dr. Daum, you did ask about what data we do have. So, George, you had put up the HIV adult slide. This is a study that was -- because you're talking about transmission and say, well, what's the end result if it gets transmitted to somebody, and the DMID study 98005 done in collaboration with the NIH was done and is presented in the BLA, and in that study of 50-some adults by placebo or vaccine, shedding was looked at in the first three days, seven to ten days, and a third time subsequent to that.

It's in the short set. Okay, great.

So shedding was done on day three to five, seven to ten, and day 28 to 35, and the results are shown, and there was shedding of Influenza B virus in one HIV infected subject on day five, and nobody in the further days when culturing was done.

Now, in the published literature not presented in the BLA, a very similar study design in pediatric HIV done by the NIH in collaboration with us, and in that study there was no prolonged shedding either in the vaccine to children. There were 24 HIV infected children, and they were one to eight years of age with a mean of 4.2 years.

CHAIRMAN DAUM: Thank you, Dr. Mendelman.

Dr. Snider and then Dr. Steinhoff on this issue, and maybe we can move on to something besides shedding at that point unless there are issues the committee has not addressed as yet.

Dr. Snider.

DR. SNIDER: I think maybe my question has been answered, but let me just phrase it a different way. I seem to recall prior to lunch there was a quick statement made about other studies that were not part of the BLA having been done that look at transmission and demonstrated no transmission.

So I guess the question is: is there any other data that has not yet been presented about transmission or lack thereof that needs to be brought before the committee?

CHAIRMAN DAUM: Let's ask Dr. Mink first for a comment and then the sponsor.

DR. MINK: The data that we have for evaluating transmissibility is the Wyeth-Lederle transmissibility study in Finland, which we presented to you after a total review.

The other data, I actually think you

have already seen data from the sponsor. They are historical. The table that they presented they said was based on historical data.

So I'm not aware of any other data that has been submitted for review.

CHAIRMAN DAUM: Thank you.

DR. MINK: And I should have seen it probably.

CHAIRMAN DAUM: Are there other data?

Thank you. I think that answers that question.

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

DR. STEINHOFF: The only comment I wanted to make was to follow up on something that Dr. Katz said. If you look at the literature about household and family transmission of wild type influenza virus, numerous studies show that the transmission rate is between 20 and 30 percent in a family setting of wild type virus contrasted to what I'm hearing is somewhere between one and five percent from the Finland study depending on what you pick.

So there is a relative ratio that one can consider.

CHAIRMAN DAUM: Thank you, Mark.

The historical data that are being referred to can be found in Table 36, Dr. Overturf reminds us, of which presentation?

DR. OVERTURF: It's Table 36 of the sponsor's presentation.

CHAIRMAN DAUM: Thank you very much.

Ms. Fisher, germane to this issue?

MS. FISHER: Well, I just have to make a comment about Sam Katz's comment about comparing the life virus flu vaccine to the live polio vaccine, and that is that the flu is not polio, and we have moved away from the live virus polio vaccine to a killed vaccine precisely to prevent vaccine induced polio.

So I don't think the comparison is correct.

CHAIRMAN DAUM: Thank you very much.

Can we perhaps move on? Are there other points about transmissibility that haven't been addressed? I think we've had a pretty thorough discussion about it.

Dr. Snider, did you wish --

DR. SNIDER: Not about transmissibility.

CHAIRMAN DAUM: Well, Dr. Markovitz is