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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	*Definition*
AFI	Any Febrile Illness
CAIV	Cold-Adapted Influenza Vaccine
CBER	Centers for Biologics and Evaluation and Research
CDC-ILI	Centers for Disease Control Influenza-Like Illness
CI	Confidence Intervals
CRL	Complete Response Letter
CSR	Clinical Study Reports
DOD-ILI	Department of Defense Influenza-Like Illness
FluMist	Trade Name for Influenza Virus Vaccine Live, Intranasal Manufactured by MedImmune Vaccines, Inc
FURI	Febrile Upper Respiratory Illness
HA	Hemagglutinin
HID_{50}	Median Human Infectious Dose
HMO	Health Maintenance Organization
KP	Kaiser Permanente
MAE	Medically Attended Events
MDV	Master Donor Virus
MAARI	Medically Attended Acute Respiratory Illness
MSG	Monosodium Glutamate
NA	Neuraminidase
NAF	Normal Allantoic Fluid
OME	Otitis Media with Effusion
OPV	Oral Polio Virus
RAD	Reactive Airways Disease
OTC	Over the Counter
RR	Relative Risk
SAE	Serious Adverse Events
SFI	Severe Febrile Illness
SOB	Shortness of Breath
SPF	Specific Pathogen-Free
SPG	Sucrose, Potassium Phosphate, and Monosodium Glutamate
$TCID_{50}$	Median Tissue Culture Infectious Dose
URI	Upper Respiratory Infection
USPHS	U.S. Public Health Service
VRBPAC	Vaccines and Related Biological Products Advisory Committee

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1. OVERVIEW

1.1. FluMist's Regulatory Review History

Influenza virus vaccine live, intranasal (FluMist™) is an intranasally administered trivalent vaccine intended for active immunization for the prevention of influenza. In a July 2001 meeting, the Vaccines and Related Biological Products Advisory Committee (VRBPAC) considered safety and efficacy data accumulated for FluMist and concluded that:

- Data were adequate to establish the efficacy and effectiveness of FluMist in the pediatric, adolescent, and adult population, specifically, from 15 months through 64 years of age.
- Data were not adequate at that time to establish the safety of FluMist based on remaining concerns regarding asthma (possible signal observed in 18–35 month olds in one study), pneumonia, and lack of concurrent immunization data for the children <18 months of age.

Since the 2001 VRBPAC Meeting, MedImmune Vaccines has interacted with CBER through responses to two Complete Response Letters (CRL) and discussions which have lead to the following outcomes:

- Evaluation of integrated data across all studies and additional evaluation of Study AV019 suggest a possible increase in medically attended asthma/wheezing events after FluMist administration in children up to 59 months of age (Section 9 of this document). The magnitude of the apparent increase was small and clinical impact was generally mild. No evidence for an increase was observed in children over the age of 59 months or in adolescents and adults. Until additional information regarding asthma/wheezing in children younger than 5 years is available, this population will not be included in the requested label. MedImmune Vaccines will eventually seek an indication for healthy children 19 months through 59 months of age and plans to discuss a proposed clinical development plan for these children with CBER in the near future.

- Because of the asthma/wheezing "signal", MedImmune Vaccines has modified the requested indication for FluMist to: *"healthy individuals age 5 years (60 months) through 64 years."* In addition, the label will exclude individuals with underlying medical conditions such as: asthma or recurrent medically attended wheezing episodes, immunodeficiencies or chronic immunosuppression, other chronic pulmonary or cardiovascular disorders, chronic metabolic disease (including diabetes), renal dysfunction, and hemoglobinopathies. (Section 2).
- Assessment of final data for pneumonia across all studies shows that there is no increase in the incidence of pneumonia observed in FluMist recipients (Section 7).
- It is anticipated that the change in the requested indicated age (60 months through 64 years) removes the necessity for concurrent pediatric immunization data in consideration of this application. MedImmune Vaccines is currently evaluating FluMist when given concurrently with MMRII® and VARIVAX® vaccines and plans subsequent studies with other pediatric vaccines (Section 8).
- Data from a study of transmission of vaccine virus in a day-care setting in Finland were provided to CBER as part of the CRL responses (Section 11). These data represent a "worst-case" scenario, from a study designed to optimize the occurrence and detection of transmission. As expected, the study documented that transmission can occur at a low rate. The *ts* and *ca* phenotypes were maintained in shed and transmitted virus.
- CBER has identified that the safety database for healthy persons 50–64 years of age is not as robust (N = 511) when compared to other age groups. However, FluMist data in healthy persons by age (Section 5.2.1) show a similar safety profile in healthy adults 50–64 years compared to those less than 50 years of age. MedImmune Vaccines has agreed to conduct an off-season, placebo-controlled post-licensure study in healthy adults in this age group to provide additional controlled safety data as a benchmark for post-marketing safety surveillance in this population.

1.2. Outline of Presentation

In this presentation to the VRBPAC, MedImmune Vaccines will review data in support of the following indication:

- *FluMist is indicated for active immunization for the prevention of disease caused by influenza A and B viruses in healthy individuals ages 5 years (60 months) through 64 years.*

This briefing document is intended to: 1) summarize the relevant data regarding FluMist, its clinical development, efficacy/effectiveness and safety profile, 2) address each of the topics outlined above, and 3) summarize data on other selected safety topics discussed at the previous VRBPAC meeting.

The outline of the Briefing Document is as follows:

- Overview
- Product Description
- Overview of Clinical Trials of FluMist
- Summary of Efficacy and Effectiveness in Children and Adults
- Overview of General Safety
  - Data on Revaccination
  - Pneumonia
  - Asthma/Wheezing
  - CNS Events
- Data on Vaccine Virus Transmission
- Phenotypic and Genotypic Stability of Vaccine Virus
- Summary and Conclusions

2. PRODUCT DESCRIPTION AND PROFILE

Description

Influenza Virus Vaccine Live, Intranasal (FluMist™) is an intranasally administered trivalent vaccine intended for active immunization for the prevention of influenza.

The vaccine contains Type A/H1N1, Type A/H3N2, and Type B influenza strains that are (a) antigenically representative of influenza viruses that are expected to circulate in humans during the relevant influenza season; (b) cold-adapted (*ca*) [i.e., they replicate efficiently at 25°C, a temperature that is restrictive for replication of many wild-type influenza viruses]; (c) temperature-sensitive (*ts*) [i.e., they are highly restricted in replication at 37°C (Type B strains) and 39°C (Type A strains), temperatures at which many wild-type influenza viruses grow efficiently]; and (d) attenuated (*att*) so as not to produce classical influenza-like illness. Each 0.5 mL dose is formulated to contain $10^{6.5\text{-}7.5}$ $TCID_{50}$ (median tissue culture infectious doses) of each of the three influenza virus strains recommended by the U.S. Public Health Service (USPHS) for the relevant influenza season.

Each of the three influenza strains contained in FluMist is produced by genetic reassortment of a wild-type influenza virus and a Master Donor Virus (MDV). The MDV (A/Ann Arbor/6/60 and B/Ann Arbor/1/66) were developed by Massaab et al. using serial passage at sequentially lower temperatures in specific pathogen-free (SPF) primary chick kidney cells. During this process, the MDV acquired mutations in six gene segments encoding internal viral proteins; these mutations conferred *ca*, *ts*, and *att* phenotypes upon the MDV. For each of the three strains in FluMist, the six internal gene segments responsible for the *ca*, *ts*, and *att* phenotypes are derived from the MDV, and the two gene segments that encode the two surface proteins, hemagglutinin (HA) and neuraminidase (NA) are derived from a wild-type influenza virus recommended by the USPHS for inclusion in the vaccine formulation. Thus, the three viruses contained in FluMist maintain the replication characteristics and phenotypic properties of the MDV but express the HA and NA of the three representative wild-type viruses that are expected to circulate during the relevant influenza season.

FluMist is produced by inoculating each of the three reassortant viruses into SPF eggs that are incubated to allow for vaccine virus replication. The allantoic fluids of these eggs are harvested, clarified by centrifugation, and stabilized with buffer containing

sucrose, potassium phosphate, and monosodium glutamate (SPG). Virus harvests from the three strains (H1N1, H3N2, and B) are subsequently blended and diluted to strength with normal allantoic fluid (also derived from SPF eggs) to produce trivalent bulk vaccine. The bulk vaccine is then filled into individual intranasal spray devices, labeled, and stored at ≤ -15°C. Each lot of viral harvest is tested for attenuation in ferrets and is also tested extensively by a battery of in vitro and in vivo methods for the presence of adventitious agents.

Gentamicin sulfate is added early in the manufacturing process to prepare reassortant viruses, at which time residual gentamicin is present at a calculated concentration of approximately 1 μg/mL. Later steps of the manufacturing process do not use gentamicin, so that with subsequent dilution the residual concentration in the final product is <0.015 μg/mL (limit of detection of the assay). FluMist does not contain thimerosal or other preservatives.

Each pre-filled FluMist sprayer contains a single 0.5 mL dose and is delivered as a fine mist. The spray device has a teflon tip with a one way valve that produces a large-particle aerosol that is deposited in the nose and nasopharynx. When thawed for administration, FluMist is a colorless to pale yellow liquid and is clear to slightly cloudy.

FluMist should be stored at -15°C (5°F) prior to use. Generally, FluMist is thawed immediately prior to administration by holding the sprayer in the palm of the hand. Alternatively, FluMist may be thawed in a refrigerator and stored at 2°C to 8°C (36°F to 46°F) for no more than 24 hours prior to use. Approximately half of the dose from a single FluMist sprayer (0.25 mL) is administered into each nostril while the recipient is in an upright position. The tip of the sprayer is inserted just inside the nose and the plunger is depressed to spray the first half of the dose. The dose-divider clip is then removed from the plunger of the sprayer to administer the second half of the dose into the other nostril.

FluMist will be supplied as a single-use, pre-filled intranasal spray device in 10-sprayer packages.

Clinical Evaluation of FluMist

FluMist has been evaluated in a total of 20 clinical trials in which a total of 20,228 participants received 28,979 doses of FluMist, including 16,260 healthy children 1 to 17 years of age (2,581 of whom had a prior history of asthma/wheezing) and 3,805 healthy

adults 18 to 64 years of age (60 of whom had a prior history of asthma/wheezing) who received at least one dose of vaccine. Second and third annual doses have been given to 3,003 and 642 children, respectively. In randomized, placebo-controlled trials, 8,339 healthy children (1,547 of whom had a prior history of asthma/wheezing) and 3,314 healthy adults (36 of whom had a prior history of asthma/wheezing) received vaccine. Clinical efficacy and effectiveness estimates and reported adverse events are described elsewhere in this briefing document (Sections 4 and 5).

Requested Indication

The primary potential indication for FluMist will be for active immunization for the prevention of disease caused by influenza A and B viruses in healthy children, adolescents, and adults age 5 years (60 months) through 64 years.

Dosage and Administration

FluMist should be administered according to the following schedule:

Age Group	Dosage Schedule
Children 5 through 8 years	0.5 mL (1 or 2 doses)*
Children and Adolescents 9 through 17 years	0.5 mL (1 dose)
Adults 18 through 64 years	0.5 mL (1 dose)

* Two doses of FluMist administered approximately 60 days apart (range 46 to 74 days) are recommended for healthy children under 9 years of age who have not previously received FluMist or inactivated influenza virus vaccine. Limited data are available concerning the degree of protection in children who receive one primary dose.

Annual vaccination against influenza is recommended for optimal protection.

Potential Contraindications

- A history of hypersensitivity, especially anaphylactic reactions, to any component of FluMist, including eggs or egg products.
- Children or adolescents who are receiving aspirin therapy or other salicylates (because of the association of aspirin and wild-type influenza infection with Reye syndrome).
- Individuals with known or suspected immune deficiency diseases and conditions such as combined immunodeficiency, agammaglobulinemia, human immunodeficiency virus infection, thymic abnormalities, malignancy, leukemia, or lymphoma.

- Individuals who may be immunosuppressed or have altered or compromised immune status as a consequence of treatment with systemic corticosteroids, alkylating drugs, antimetabolites, radiation, or other immunosuppressive therapies. [NOTE: Most experts agree that steroid therapy is not a contraindication to the administration of a live virus vaccine when steroids are given for short-term therapy (i.e., <2 weeks), in low to moderate doses, as alternate-day treatment with short-acting preparations, as maintenance physiologic doses (replacement therapy), or administered topically, by aerosol, or by intra-articular, bursal, or tendon injection. In these instances, the clinical judgment of the health-care provider should prevail.]
- Individuals who have a prior history of Guillain-Barré syndrome.

Potential Warnings

- The safety and efficacy of FluMist in persons with asthma or history of recurrent wheezing illness has not been established. Data are limited regarding the risk of exacerbation of underlying reactive airways disease following FluMist administration. Until additional data are available, FluMist should not be administered to persons with asthma, or to children who have had recurrent medically attended wheezing illness.
- The safety and efficacy of FluMist in patients with chronic underlying medical conditions that may place them at a higher risk of complications following wild-type influenza have not been established. Such patients include but are not limited to adults and children with chronic disorders of the pulmonary and cardiovascular systems, including asthma; adults and children who required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes), renal dysfunction, or hemoglobinopathies; and adults and children with congenital or acquired immunosuppression caused by underlying disease or immunosuppressive therapy.
- Health care providers should be aware that there is a potential risk for allergic reactions in individuals with a history of hypersensitivity to aminoglycosides (gentamicin) or potential reactions to monosodium glutamate (MSG) since gentamicin and MSG are used in the manufacturing process of FluMist.
- The safety and efficacy of FluMist in pregnant women have not been established. Therefore, FluMist should not be administered during pregnancy.

Potential Precautions

- Epinephrine for injection (1:1000) or comparable treatment should be readily available in the event of an acute anaphylactic reaction following vaccination. The healthcare provider may enhance prevention of allergic or other adverse reactions by reviewing the patient's history for possible sensitivity to influenza vaccine components, including eggs.
- Because of the potential for very low-level transmission of vaccine, FluMist recipients should avoid close contact with immunocompromised individuals whenever feasible for three weeks following vaccination of young children and for one week in vaccinated adults.
- Administration of FluMist should be postponed until after the acute phase of febrile and/or respiratory illnesses.
- The safety and efficacy of FluMist when administered concurrently with antiviral compounds that are active against influenza A and/or B viruses have not been established. Based on the potential for interference between such compounds and FluMist, and in order to maintain the protective efficacy of FluMist, it is advisable that FluMist not be administered until 48 hours following the cessation of antiviral therapy and that antivirals not be administered until two weeks following administration of FluMist unless medically indicated.

Concurrent Administration with Other Vaccines

The safety and immunogenicity of FluMist when administered concurrently with other vaccines have not been established, nor has the degree to which FluMist may affect the safety and immunogenicity of other vaccines when administered concurrently with FluMist. Therefore, FluMist should not be administered concurrently with other vaccines. Completed clinical studies of FluMist to date excluded participants who received any live virus vaccine within one month prior to enrollment and any inactivated or subunit vaccine within two weeks of enrollment; therefore, health care providers should adhere to these intervals when administering FluMist.

3. REVIEW OF FLUMIST CLINICAL PROGRAM: OVERALL STUDIES AND NUMBER OF PARTICIPANTS

The total number of participants who have received one, two, or more doses of FluMist are presented in Table 1. Among the 20,228 participants, 10,321 were 60 months to 17 years of age and 3,805 were 18 through 64 years of age. The numbers contributing to this table are from those studies for which final clinical study reports (CSRs) have been submitted to CBER. A complete list of those studies is provided in Table 2.

Table 1
Total Number of Doses of FluMist and Placebo Administered in Completed Clinical Study Reports by Age Group

Age Category	Doses of FluMist[a]						Total Doses of Placebo
	First	Second	Third	Fourth	Fifth	Total	
1–2 years	1285	756				2041	730
2–4 years	4678	2889	475	188	1	8231	2593
5–8 years	4418	2643	365	367	1	7794	1970
9–17 years	5903	1028				6931	1371
18–29 years	1081	29				1110	458
30–49 years	2241	9				2250	1037
50–64 years	511					511	209
65 years and older	111					111	101
Total All Studies	**20228[b]**	**7354**	**840**	**555**	**2**	**28979**	**8469**

[a] The fourth and fifth doses represent vaccination for a third annual season.

[b] Includes 171 children in Studies AV002 and AV002-2 who received 10^4, 10^5 and 10^6 $TCID_{50}$ dosages rather than 10^7 $TCID_{50}$, 28 HIV-infected adults (Study DMID #98-005) and 24 children 9–17 years of age with moderate to severe asthma who received FluMist.

Table 2
(1 of 4)
Completed Clinical Studies in Support of FluMist

Study	Design	Participants	Study Group	Number Enrolled	Doses	Objectives
AV001	Phase 1 Randomized, Double-Blind, Placebo-Controlled	Healthy Adults, 18–65 years of age	FluMist Placebo	181 58	1 Dose	1. Safety and immunogenicity 2. Spray versus Drops
AV002	Phase 1/2 Randomized, Double-Blind, Placebo-Controlled	Healthy Children, 18–71 months of age	FluMist Placebo	155 83	1 Dose	1. Safety and immunogenicity 2. Dose response 3. Spray versus drops
AV002-2	Phase 2 Randomized, Double-Blind, Placebo-Controlled	Healthy Children, 18–71 months of age	FluMist Placebo	79 39	1 Dose	1. Safety and immunogenicity 2. Dose response
AV003	Phase 3 Randomized, Double-Blind, Placebo-Controlled	Adults 18–41 years of age serosusceptible to at least one influenza strain	FluMist + IM placebo Spray placebo and TIV (IM) Placebo (Spray and IM)	36 33 34	1 Dose	1. Protection against laboratory-documented influenza 2. Safety and immunogenicity
AV004	Phase 2 Open Label, Randomized, Placebo-Controlled	Healthy Adults, 18–65 years of age	FluMist Placebo	15 5	1 Dose	1. Safety of 1995–1996 strains in healthy adults prior to escalating to a 10^7 $TCID_{50}$ dose in Study AV002
AV005	Phase 2 Randomized, Double-Blind, Placebo-Controlled	Healthy Adults, 18–45 years of age	FluMist Placebo	16 16	2 Doses	1. Safety of two doses at 10^7 $TCID_{50}$ of 1996–1997 strains in adults

Table 2
(2 of 4)
Completed Clinical Studies in Support of FluMist

Study	Design	Participants	Study Group	Number Enrolled	Doses	Objectives
AV006 Year One	Phase 3 Randomized, Double-Blind, Placebo Controlled	Healthy Children, 15–71 months of age	FluMist Placebo	1070 532	1 or 2 Doses	1. Efficacy of FluMist to prevent culture-confirmed influenza 2. Immunogenicity in a subset of participants
AV006 Year Two	Phase 3 Randomized, Double-Blind, Placebo Controlled	Healthy Children, 15–71 months of age at time of enrollment in Year One	FluMist Placebo	917 441	1 Dose	1. Efficacy of FluMist to prevent culture-confirmed influenza 2. Immunogenicity in a subset of participants
AV007	Phase 3 Randomized, Double-Blind, Placebo-Controlled	Healthy Children, 12–36 months of age	FluMist Placebo	400 100	2 Doses	1. Lot consistency (3 lots) 2. Bridging to vaccine used in efficacy Study AV006
AV008	Phase 3 Randomized, Double-Blind, Placebo-Controlled	Adults ≥65 Years, ≥1 Other high-risk factor	FluMist + TIV Placebo + TIV	100 100	1 Dose	1. Safety of co-administration of FluMist with TIV in high-risk adults
AV009	Phase 3 Randomized, Double-Blind, Placebo-Controlled	Healthy working adults, 18–64 years of age	FluMist Placebo	3041 1520	1 Dose	1. Safety 2. Effectiveness in reducing influenza-like illness, absenteeism, health care utilization
AV010	Phase 3 Randomized, Double-Blind, Placebo-Controlled	Children with moderate to severe asthma, 9–17 years of age	FluMist Placebo	24 24	1 Dose	1. Safety of FluMist in children with moderate to severe asthma

Table 2
(3 of 4)
Completed Clinical Studies in Support of FluMist

Study	Design	Participants	Study Group	Number Enrolled	Doses	Objectives
AV011	Phase 3 Randomized, Vaccine Challenge	Healthy children from Study AV006	Prior FluMist Prior Placebo	144 78	1 Dose	1. Efficacy of FluMist to prevent shedding of vaccine virus (H1N1)
AV012 Year One	Phase 3 Open Label, Unvaccinated control communities	Healthy children 18 months – 18 years of age conducted at Scott & White HMO, Temple, Texas	FluMist	4298	1 Dose	1. Safety and herd immunity for control of epidemic influenza
AV012 Year Two	Phase 3 Open Label, Unvaccinated control communities	Healthy children 18 months – 18 years of age conducted at Scott & White HMO, Temple, Texas	FluMist	5251	1 Dose	1. Safety and herd immunity for control of epidemic influenza
AV014	Phase 3 Randomized, Double-Blind	Healthy children 12–42 months of age	FluMist	225	2 Doses	1. Comparison of safety, tolerability and immunogenicity of FluMist from two manufacturing facilities
AV015	Phase 3 Open Label	Healthy children who participated in AV006 approximately 3–8 years of age at time of re-enrollment	FluMist	949	1 Dose or 2 Doses	1. Safety and tolerability for third year of vaccination. 2. Safety and tolerability of primary vaccination with FluMist in prior placebo recipients
AR001	Phase 3 Randomized, Double-Blind	Adults and children	FluMist rFluMist[a]	224 225	1 Dose if ≥9 years, 2 Doses if 1–8 years	1. Comparison of classical FluMist versus recombinant FluMist (rFluMist)

[a] rFluMist = FluMist produced by recombinant methods; only one strain of rFluMist, A/Shenzhen/227/95 (H1N1), was made using recombinant methodology.

Table 2
(4 of 4)
Completed Clinical Studies in Support of FluMist

Study	Design	Participants	Study Group	Number Enrolled	Doses	Objectives
DMID #98-005 (NIH)	Phase 2 Randomized, Double-Blind, Placebo-Controlled	Adults 18–50 years of age	HIV-infected FluMist Placebo HIV-negative FluMist Placebo	 28 29 27 27	1 Dose	1. Safety, vaccine virus shedding and immunogenicity in HIV-infected adults 2. Effects on HIV RNA and CD4 counts
D145-P500 Wyeth-Lederle Vaccines, Non-IND	Randomized, Double-Blind, Placebo-Controlled	Healthy children 8–36 months of age attending day care in Finland	FluMist Placebo	98 99	1 or 2 [2nd dose optional, open label]	1. Safety 2. Transmissibility
AV019	Randomized, Double-Blind, Placebo-Controlled	Healthy children 1–17 years of age conducted at Kaiser Permanente HMO, Northern California	FluMist Placebo	6473: 3769 (1–8 years) 2704 (9–17 years) 3216: 1868 (1–8 years) 1348 (9–17 years)	2 doses (1–8 years) 1 dose (9–17 years)	1. Safety

4. SUMMARY OF EFFICACY AND EFFECTIVENESS

Introduction

Efficacy of FluMist against culture-confirmed influenza disease was assessed in three studies: a field trial (AV006) in children, a vaccine-strain challenge study (AV011) in children, and in a wild-type influenza virus challenge study in adults (AV003).

Effectiveness of FluMist, defined as a reduction in influenza and influenza-like illness-associated morbidity, absenteeism, and health care utilization, was assessed in two studies: the same field trial in children (AV006) as well as in a field trial in adults (AV009).

4.1. Efficacy in Healthy Children

Study AV006 was a multi-center, randomized, double-blind, placebo-controlled trial performed in healthy U.S. children to evaluate the efficacy of FluMist against culture-confirmed influenza over two successive seasons. The primary endpoint of the trial was the prevention of culture-confirmed influenza illness. A total of 1602 healthy children 15 to 71 months of age were randomized 2:1 (vaccine:placebo) during the first year of the study. The surveillance period for efficacy began 15 days after the receipt of the first dose of vaccine or placebo.

In the first year of Study AV006, both type A (H3N2) and type B strains circulated. As shown in Table 3, when compared with placebo recipients, FluMist recipients experienced a significant reduction in the incidence of (1) culture-confirmed influenza (efficacy 92.6%, 95% CI: 87.3, 95.7); (2) culture-confirmed influenza associated with fever (efficacy 95.0%, 95% CI: 90.0, 97.5) and (3) culture-confirmed influenza associated with acute otitis media (efficacy 97.5%, 95% CI: 85.5, 99.6). The efficacy of culture-confirmed influenza associated with lower respiratory illness was not statistically significant in Year One (efficacy 83.4%, 95% CI: -15.4, 97.6), but was in Year Two (efficacy 100%, 95% CI: 77.0, 100) (Table 3). In addition, in the subset of children who were specifically enrolled to receive a single dose of FluMist (n=189) or placebo (n=99), FluMist was associated with an 88.8% efficacy (95% CI: 64.5, 96.5) against culture confirmed influenza (any strain), 86.9% efficacy (95% CI: 46.6, 96.8) against type A (H3N2), and 91.3% efficacy (95% CI: 45.6, 98.6) against type B.

A total of 1358 of the original 1602 children (85%) returned for the second year of Study AV006. Children remained in the same treatment group as in Year One and received a single dose of FluMist or placebo. The primary endpoint of the trial remained the prevention of culture-confirmed influenza illness. However, during the second year of Study AV006, the epidemic H3N2 strain, A/Sydney/05/97, differed antigenically from A/Wuhan/359/95, the H3N2 strain included in the vaccine. The FluMist group demonstrated similar efficacy as in Year One for culture-confirmed influenza (87.1%, 95% CI: 77.7, 92.6); culture-confirmed influenza associated with fever (89.3%, 95% CI: 80.4, 94.2), and culture-confirmed influenza associated with otitis media (94.3%, 95% CI: 78.1, 98.5) (Table 3).

Because wild-type A (H1N1) did not circulate in the U.S. during either year of Study AV006, a separate study (Study AV011) was carried out to estimate the protective efficacy against challenge with the H1N1 vaccine strain. The study was a multi-center, randomized, double-blind, challenge study conducted following the conclusion of the second year of Study AV006 in a subset of 222 children age 34 to 91 months who had received FluMist (N=144) or placebo (N=78) during Study AV006. The objective of this study was to estimate the protective efficacy of the vaccine against the H1N1 virus subtype by detection of vaccine virus shedding during any of the four days following vaccination. The efficacy of FluMist against this challenge was 82.9% (95% CI: 60.2, 92.7) (Table 3).

Table 3
Efficacy of FluMist in Healthy Children

Study	Endpoint	Incidence n (%)		% Efficacy	(95 % CI)
		FluMist	Placebo		
Study AV006 Year One		**N=1070**	**N=532**		
	Culture-confirmed influenza	14 (1.3)	94 (17.7)	**92.6**	(87.3, 95.7)
	Associated febrile illness	8 (0.7)	80 (15.0)	**95.0**	(90.0, 97.5)
	Associated otitis media	1 (0.1)	20 (3.8)	**97.5**	(85.5, 99.6)
	Associated lower respiratory illness	1 (0.1)	3(0.6)	**83.4**	(-15.4, 97.6)
Study AV006 Year Two		**N= 917**	**N=441**		
	Culture-confirmed influenza	15 (1.6)	56 (12.7)	**87.1**	(77.7, 92.6)
	Associated febrile illness	12 (1.3)	54 (12.2)	**89.3**	(80.4, 94.2)
	Associated otitis media	2 (0.2)	17 (3.9)	**94.3**	(78.1, 98.5)
	Associated lower respiratory illness	0 (0)	8 (1.8)	**100**	(77.0, 100)
Study AV011[a]		**N= 142**	**N=77**		
	Type A/H1N1 vaccine virus shedding	6 (4.2)	19 (24.7)	**82.9**	(60.2, 92.7)

[a] Two prior FluMist recipients and one prior placebo recipient were not evaluable for analysis.

4.1.1. Efficacy in Healthy Children by Age

Table 4 presents the efficacy against any culture-confirmed influenza and the number of cases that contributed to the analyses of efficacy by age for Year One of Study AV006. Similar information for Year Two of Study AV006 is presented in Table 5.

Table 4
Number of Cases and Totals Included in the Efficacy of FluMist by Age – Study AV006 Year One

Age (mos.)	FluMist n/N	Placebo n/N	Total n/N	Any Influenza % Efficacy (95% CI)
<24	4/173	15/99	19/272	84.7 (57.5, 94.6)
24–35	2/225	31/134	33/359	96.2 (85.8, 99.0)
36–47	5/231	16/96	21/327	87.0 (66.8, 94.9)
48–59	0/224	18/108	18/332	100 (89.9, 100)
≥60	3/217	14/95	17/312	90.6 (70.3, 97.1)

Table 5
Number of Cases and Totals Included in the
Efficacy of FluMist by Age – Study AV006 Year Two

Age (mos.)	FluMist n/N	Placebo n/N	Total n/N	Any Influenza % Efficacy (95% CI)
<24	0/0	0/0	0/0	NA
24–35	2/159	7/87	9/246	84.4 (35.2, 96.3)
36–47	4/186	15/108	19/294	84.5 (56.8, 94.5)
48–59	2/197	10/77	12/274	92.2 (69.0, 98.0)
≥60	7/375	24/169	31/544	86.9 (70.8, 94.1)

4.2. Effectiveness in Healthy Children

Study AV006 also measured the overall effectiveness of FluMist for the entire study population in reducing influenza and influenza-like illness (febrile illness and febrile otitis media with antibiotic use), missed days of day care/school, parental lost work days, and health care provider visits. In the entire study population, for children with influenza positive cultures, there were statistically significant reductions in missed daycare/school, parental lost work days and health care provider visits in Year One and Year Two (Table 6). Statistically significant reductions in febrile otitis media with antibiotic use (regardless of influenza culture results) were observed in both years.

Table 6
Effectiveness of FluMist in Healthy Children

Study	Endpoint	Rate per Participant		Percent Reduction	p-value[a]
		FluMist	Placebo		
Study AV006 Year One	**Febrile illness with antibiotic use**[b]	0.31	0.46	**31.0**	<0.01
	Febrile otitis media with antibiotic use[b]	0.14	0.22	**35.0**	<0.01
	Missed daycare/preschool/school days				
	All Illness[b]	0.76	0.84	**9.4**	0.34
	Culture positive illness	0.01	0.17	**94.4**	<0.01
	Parental lost work days				
	All Illness[b]	0.26	0.31	**16.8**	0.24
	Culture positive illness	<0.01	0.08	**97.7**	<0.01
	Healthcare provider visits				
	All Illness[b]	1.20	1.39	**13.4**	0.02
	Culture positive illness	0.01	0.14	**93.9**	<0.01
Study AV006 Year Two	**Febrile illness with antibiotic use**[b]	0.30	0.34	**10.6**	0.18
	Febrile otitis media with antibiotic use[b]	0.11	0.13	**20.9**	0.04
	Missed daycare/preschool/school days				
	All Illness[b]	0.93	1.11	**16.6**	0.01
	Culture positive illness	0.02	0.23	**92.5**	<0.01
	Parental lost work days				
	All Illness[b]	0.29	0.32	**8.7**	0.37
	Culture positive illness	0.01	0.07	**87.8**	<0.01
	Healthcare provider visits				
	All Illness[b]	0.95	1.02	**7.0**	0.18
	Culture positive illness	0.01	0.09	**88.9**	<0.01

[a] Unadjusted for multiple comparisons, Wilcoxon Rank Sum test.

[b] For all participants with illness events regardless of whether a culture was obtained.

4.3. Efficacy in Healthy Adults

Study AV003 was a multi-center, randomized, double-blind, placebo-controlled trial performed in 92 healthy adults 18 to 41 years of age who were seronegative to at least one strain included in the vaccine. The primary endpoint of the study was to compare the efficacy of FluMist and a licensed inactivated influenza vaccine against laboratory documented influenza illness after challenge with wild-type influenza viruses. Adults were randomized to receive either FluMist (N=29), inactivated influenza virus vaccine (N=32), or placebo (N=31). Following subsequent intranasal administration of the wild-type challenge viruses, the overall efficacy of FluMist against laboratory-documented influenza illness was 85% compared to placebo (Table 7).

Table 7
Efficacy of FluMist in Healthy Adults

Study AV003					
Endpoint	**Group**	**N**	**Incidence n (%)**	**% Efficacy**	**(95% CI)**
Laboratory Documented Influenza against Wild-Type Challenge	FluMist	29	2 (7)	**85**	(28, 100)
	Placebo	31	14 (45)	**-**	-
	TIV	32	4 (13)	**71**	(2, 97)

4.4. Effectiveness in Healthy Adults

Study AV009 was a multi-center, randomized double-blind, placebo-controlled trial designed to evaluate the effectiveness of FluMist in the reduction of (1) illness; (2) illness-associated days of absenteeism from work; and (3) days of health-care utilization during influenza outbreaks. A total of 4,561 healthy adults 18 to 64 years of age (2,489 women and 2,072 men) were randomized 2:1 (vaccine:placebo). The peak influenza outbreak period at each site was based on community surveillance. Three febrile influenza-like illness definitions were prospectively assessed: any febrile illness (AFI), severe febrile illness (SFI), and febrile upper respiratory illness (FURI). Two more stringent febrile illness definitions were retrospectively assessed: Centers for Disease Control Influenza-Like Illness (CDC-ILI) and the Department of Defense Influenza-Like Illness (DOD-ILI). Cultures for influenza virus from individual subjects were not obtained. Adults were characterized as having AFI if they had symptoms for at least two consecutive days with fever on at least one day and if they had two or more symptoms (fever, chills, headache runny nose, sore throat, cough, muscle aches, tiredness/weakness) on at least one day. SFI was defined as having at least three consecutive days of symptoms, at least one day of fever, and two or more symptoms on at least three days. FURI was defined as at least two consecutive days of upper respiratory symptoms (runny nose, sore throat, or cough), fever on at least one day, and two symptoms on at least one day. CDC-ILI was defined as fever and cough or fever and sore throat on consecutive days. DOD-ILI was defined as fever and cough or fever and chills on consecutive days. The predominant circulating strain of influenza virus during

the trial was A/Sydney/05/97 (H3N2), a variant strain which differed antigenically from the A/Wuhan (H3N2) strain contained in FluMist.

As shown in Table 8, reductions were seen in all endpoints measured during the site-specific outbreak periods; FluMist recipients experienced a 23% reduction in days of illness for AFI, a 27% reduction in days of illness for SFI, a 25% reduction in the days of illness for FURI, a 30% reduction in the days of illness for CDC-ILI, and a 32% reduction in the days of illness for DOD-ILI compared to placebo. Days of prescription antibiotic use were significantly decreased across all five febrile illness definitions. Illness-associated days of missed work and days of health care provider visits were both statistically significantly decreased for four of the five illness definitions, the exception being AFI.

Table 8
Effectiveness of FluMist in Healthy Adults – Study AV009

Endpoint	FluMist N=2833	Placebo N=1420	Percent Reduction	(95% CI)
	Incidence per Participant n (%)			
Proportion with:				
Any febrile illness	373(13.2)	207 (14.6)	**9.7**	(-5.8, 22.8)
Severe febrile illness	285 (10.1)	173 (12.2)	**17.4**	(1.3, 30.8)
Febrile upper respiratory illness	240 (8.5)	154 (10.8)	**21.9**	(5.3, 35.5)
CDC-ILI	302 (10.7)	197 (13.9)	**23.2**	(9.1, 35.0)
DOD-ILI	296. (10.4)	194 (13.7)	**23.5**	(9.4, 35.4)
	Rate[a]		Percent Reduction	95% CI
Days of:				
Any febrile illness	1188.0	1541.2	**22.9**	(12.1, 32.4)
Severe febrile illness	1021.1	1404.5	**27.3**	(16.7, 36.5)
Febrile upper respiratory illness	875.7	1164.7	**24.8**	(13.5, 34.7)
CDC-ILI	846.3	1201.3	**29.6**	(19.4, 38.4)
DOD-ILI	823.9	1218.5	**32.4**	(22.7, 40.8)
Days of missed work due to:				
Any febrile illness	173.3	199.5	**13.1**	(-0.9, 25.2)
Severe febrile illness	154.7	188.3	**17.9**	(4.3, 29.5)
Febrile upper respiratory illness	107.0	149.4	**28.4**	(16.3, 38.8)
CDC-ILI	141.2	176.3	**19.9**	(6.7, 31.2)
DOD-ILI	130.8	189.9	**31.1**	(19.9, 40.7)
Days of health-care provider visits due to:				
Any febrile illness	44.0	51.5	**14.7**	(-0.3, 27.5)
Severe febrile illness	37.6	50.1	**24.8**	(11.6, 26.1)
Febrile upper respiratory illness	23.8	40.3	**40.9**	(30.1, 50.0)
CDC-ILI	34.7	43.3	**20.0**	(5.7, 32.2)
DOD-ILI	27.9	42.6	**34.4**	(22.5, 44.4)
Days of prescription antibiotic use due to:				
Any febrile illness	195.6	342.9	**42.9**	(33.1, 51.3)
Severe febrile illness	172.2	325.0	**47.0**	(37.8, 54.9)
Febrile upper respiratory illness	140.1	255.5	**45.2**	(35.2, 53.6)
CDC-ILI	172.9	275.7	**37.3**	(26.2, 46.7)
DOD-ILI	153.9	242.8	**36.6**	(25.2, 46.3)

[a] Number of days per 1,000 participants per 7-week site specific outbreak period.

4.4.1 Effectiveness in Healthy Adults by Age

The mean and median ages of the 4,561 healthy adults 18–64 years of age in Study AV009 were 38.3 and 37.7 years, respectively. Thus, the most robust comparison by age for effectiveness was performed for participants under and over 40 years of age. The effectiveness data for multiple endpoints in Study AV009 for the total population of healthy adults (all), for those under and over 40, and for those under and over 50 years of age are presented in Tables 9–13 for the five illness definitions (any febrile illness, severe febrile illness, febrile upper respiratory illness, Centers for Disease Control-ILI and the Department of Defense-ILI) for multiple effectiveness endpoints. FluMist was effective in reducing multiple illness-associated endpoints in healthy adults regardless of age. Specifically for healthy adults over 40 and over 50, there were multiple statistically significant reductions in illness-associated endpoints across all definitions of illness. For the more stringent febrile illness defined as DOD-ILI in those over 40 and over 50 years of age, there were significant reductions in the occurrence and episodes of illness.

Table 9
Percent Reduction for Any Febrile Illness (AFI) by Age

	All	**<40**	**≥40**	**<50**	**≥50**
	N=4561	N=2378	N=1875	N=3920	N=641
Illness					
Occurrence of:	9.7	9.3	11.2	10.9	-7.3
Episodes of:	10.0	7.9	14.3	11.2	-7.0
Days of:	22.9*	17.2*	32.5*	22.9*	19.8
Illness associated days of:					
Missed work	13.1	-19.1	41.8*	6.1	45.7*
Reduced work effectiveness	21.0*	4.0	42.4*	17.0*	44.0*
HCP visits	14.7	8.8	26.5*	4.9	74.3*
Antibiotic Rx	42.9*	28.8*	62.5*	40.9*	59.6*
Any Rx	39.6*	25.2*	58.5*	36.8*	58.0*
OTC	23.3*	21.2*	26.8*	25.3*	-2.3

* $p < 0.05$.

Table 10
Percent Reduction for Severe Febrile Illness (SFI) by Age

	All	<40	≥40	<50	≥50
	N=4561	N=2378	N=1875	N=3920	N=641
Illness					
Occurrence of:	17.4*	19.9*	13.4	19.5*	-7.3
Episodes of:	18.8*	19.4*	18.0	20.4*	-1.1
Days of:	27.3*	26.5*	29.0*	27.7*	21.5
Illness associated days of:					
Missed work	17.9*	-9.2	42.7*	12.0	46.1*
Reduced work effectiveness	25.6*	9.7	45.1*	22.1*	45.3*
HCP visits	24.8*	24.2*	26.6*	17.8*	71.1*
Antibiotic Rx	47.0*	38.4*	59.8*	45.7*	57.4*
Any Rx	43.7*	34.4*	56.6*	41.6*	56.7*
OTC	27.6*	28.7*	25.9*	29.8*	1.8

* $p < 0.05$.

Table 11
Percent Reduction for Febrile Upper Respiratory Illness (FURI) by Age

	All	<40	≥40	<50	≥50
	N=4561	N=2378	N=1875	N=3920	N=641
Illness					
Occurrence of:	21.9*	16.9	31.2*	23.7*	-3.4
Episodes of:	23.6*	18.9*	32.5*	25.9*	-7.8
Days of:	24.8*	16.2	37.8*	25.2*	18.0
Illness associated days of:					
Missed work	28.4*	-2.0	56.3*	26.6*	38.4*
Reduced work effectiveness	24.6*	2.8	49.8*	23.4*	32.0
HCP visits	40.9*	34.5*	52.1*	36.9*	69.2*
Antibiotic Rx	45.2*	27.2*	68.3*	45.1*	41.7*
Any Rx	40.3*	21.5*	62.6*	39.2*	46.9*
OTC	28.0*	21.3*	37.0*	29.7*	8.8

* $p < 0.05$.

Table 12
Percent Reduction for CDC-ILI by Age

	All	<40	≥40	<50	≥50
	N=4561	N=2378	N=1875	N=3920	N=641
Illness					
Occurrence of:	23.2*	20.2*	28.8*	24.4*	8.1
Episodes of:	23.6*	20.4*	29.7*	25.2*	5.0
Days of:	29.6*	18.6*	44.7*	29.9*	25.4
Illness associated days of:					
Missed work	19.9*	-13.6	48.0*	12.9	49.6*
Reduced work effectiveness	22.9*	-1.5	49.6*	18.7*	45.6*
HCP visits	20.0*	15.8	28.0*	11.1	71.1*
Antibiotic Rx	37.3*	17.3	62.0*	34.7*	56.3*
Any Rx	35.5*	14.8	59.2*	31.9*	56.0*
OTC	27.8*	20.0*	38.7*	30.6*	-1.4

* $p < 0.05$.

Table 13
Percent Reduction for Department of Defense-ILI (DOD) by Age

	All	<40	≥40	<50	≥50
	N=4561	N=2378	N=1875	N=3920	N=641
Illness					
Occurrence of:	23.5*	14.0	36.8*	21.1*	37.0*
Episodes of:	24.9*	14.8	38.8*	22.8*	37.3*
Days of:	32.4*	19.2*	47.6*	30.6*	42.4*
Illness associated days of:					
Missed work	31.1*	4.1	54.4*	23.5*	60.0*
Reduced work effectiveness	28.3*	1.1	53.8*	19.4*	63.5*
HCP visits	34.4*	33.6*	35.8*	28.9*	65.3*
Antibiotic Rx	36.6*	13.5	59.3*	35.3*	45.0*
Any Rx	34.4*	8.9	57.7*	30.9*	51.7*
OTC	32.8*	21.3*	45.9*	34.0*	25.2

* $p < 0.05$.

5. SUMMARY OF SAFETY IN HEALTHY CHILDREN AND HEALTHY ADULTS

The safety of FluMist was assessed in 20 pre-licensure clinical trials. In these studies, a total of 20,228 participants received 28,979 doses of the vaccine. This includes 16,260 healthy children 1 to 17 years of age (2,581 of whom had a prior history of asthma/wheezing) and 3,805 healthy adults 18 to 64 years of age (60 of whom had a prior history of asthma/wheezing). Overall, across randomized, placebo-controlled trials, 17,305 FluMist doses and 8,469 placebo doses have been administered. In these placebo-controlled trials, 8,339 healthy children (1,547 of whom had a prior history of asthma/wheezing) and 3,314 healthy adults (36 of whom had a prior history of asthma/wheezing) received FluMist and 4,069 healthy children (784 of whom had a prior history of asthma/wheezing) and 1,659 healthy adults (17 of whom had a prior history of asthma/wheezing) received the placebo. In all placebo-controlled studies, normal allantoic fluid (NAF) was used as the placebo.

The following sections describe 1) an overview of FluMist safety for children and adults, including revaccination and concurrent immunization and 2) specific events previously identified during VRBPAC discussions.

5.1. Safety in Healthy Children

Solicited Adverse Events in Healthy Children

Solicited adverse events were collected in four of the placebo-controlled trials (AV002, AV002-2, AV006, and AV007) conducted in healthy children 12–71 months of age (Table 14). Runny nose/nasal congestion, sore throat, irritability, headache, chills, vomiting, muscle aches, decreased activity, and low grade fever (>100°F oral) were reported in a numerically higher percentage of vaccinated children compared to placebo recipients during the 10 days after the first dose. Absolute differences ranged from 0.6% for sore throat to 12.1% for runny nose/nasal congestion and was 4.6% for low grade fever following Dose One. No difference was observed for high fever (>102°F oral). Event rates were similar in vaccinated children and placebo recipients following Dose Two, with an absolute increase >1% in FluMist recipients only for runny nose/nasal congestion (3.4%), vomiting (2.4%), cough (1.6%), decreased activity (1.5%), and chills (1.4%).

Table 14
Summary of Solicited Events Observed within 10 Days after Each Dose for FluMist and Placebo Recipients in Placebo-Controlled Studies for Healthy Children 12–71 Months of Age

	Post-Dose One				Post-Dose Two			
	FluMist 1533		Placebo 661		FluMist 1233		Placebo 513	
Event	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
Any event	1115/1517	73.5	428/659	64.9	774/1229	63.0	304/510	59.6
Cough	403/1517	26.6	187/659	28.4	386/1229	31.4	152/510	29.8
Runny nose/ Nasal congestion	881/1455	60.5	305/630	48.4	577/1229	46.9	222/510	43.5
Sore throat	131/1517	8.6	53/659	8.0	69/1229	5.6	34/510	6.7
Irritability	432/1517	28.5	176/659	26.7	237/1229	19.3	102/510	20.0
Headache	119/1455	8.2	36/630	5.7	63/1229	5.1	27/510	5.3
Chills	67/1455	4.6	26/630	4.1	47/1229	3.8	12/510	2.4
Vomiting	99/1455	6.8	28/630	4.4	87/1229	7.1	24/510	4.7
Muscle aches	79/1455	5.4	20/630	3.2	35/1229	2.8	10/510	2.0
Decreased activity	238/1455	16.4	84/630	13.3	168/1229	13.7	62/510	12.2
Fever[a]								
Temp 1	253/1517	16.7	80/659	12.1	136/1229	11.1	54/510	10.6
Temp 2	46/1517	3.0	24/659	3.6	31/1229	2.5	19/510	3.7
Temp 3	1/1517	0.1	1/659	0.2	4/1229	0.3	3/510	0.6

[a] Temp 1: Oral >100°F, rectal or aural >100.6°F, or axillary >99.6°F.
Temp 2: Oral >102°F, rectal or aural >102.6°F, or axillary >101.6°F.
Temp 3: Oral >104°F, rectal or aural >104.6°F, or axillary >103.6°F.

Other Adverse Events in Healthy Children

In addition to the solicited events, parents also reported other adverse events that occurred during the course of these four placebo-controlled trials (Table 15).

Table 15 summarizes the other adverse events that occurred within the first 10 days of vaccine or placebo. Among these healthy children 12–71 months of age, there were no medically important differences between the treatment groups.

Table 15
Adverse Events within 10 Days after Each Dose for FluMist and Placebo Recipients in Placebo-Controlled Studies for Healthy Children 12–71 Months of Age

Number of Participants Randomized	Dose One		Dose Two	
	FluMist N=1533	Placebo N=661	FluMist N=1233	Placebo N=513
Reporting Any Adverse Events	318(20.7)	109(16.5)	178(14.4)	77(15.0)
Adverse Event[a]	**n(%)**	**n(%)**	**n(%)**	**n(%)**
Body as a whole	**129(8.4)**	**46(7.0)**	**57(4.6)**	**29(5.7)**
Pain	34(2.2)	18(2.7)	7(0.6)	6(1.2)
Infection	32(2.1)	10(1.5)	22(1.8)	7(1.4)
Pain abdominal	22(1.4)	2(0.3)	9(0.7)	2(0.4)
Injury accidental	19(1.2)	5(0.8)	8(0.6)	6(1.2)
Digestive	**78(5.1)**	**30(4.5)**	**56(4.5)**	**22(4.3)**
Diarrhea	56(3.7)	22(3.3)	42(3.4)	14(2.7)
Anorexia	17(1.1)	5(0.8)	11(0.9)	4(0.8)
Respiratory	**59(3.8)**	**21(3.2)**	**32(2.6)**	**12(2.3)**
Rhinitis	21(1.4)	7(1.1)	4(0.3)	0(0.0)
Skin	**26(1.7)**	**17(2.6)**	**18(1.5)**	**6(1.2)**
Rash	16(1.0)	12(1.8)	13(1.1)	2(0.4)
Special senses	**51(3.3)**	**14(2.1)**	**47(3.8)**	**13(2.5)**
Otitis media	26(1.7)	9(1.4)	32(2.6)	8(1.6)

[a] Presented by Body System and modified COSTART Term.

Medically Attended Events in Healthy Children and Adolescents Age 1 to 17 Years

A large randomized, double-blind, placebo controlled trial in healthy children was conducted at 31 clinics in the Northern California Kaiser Permanente Health Maintenance Organization (HMO) to assess the rate of medically attended events (MAEs) within 42 days of vaccination. A total of 9,689 evaluable children 1–17 years of age were randomized 2:1 (vaccine to placebo) including 4,762 boys and 4,927 girls. Of these 9,689 children, 5,637 were 1–8 years of age and 4,052 were 9–17 years of age. Dose Two for children less than nine years of age was to be administered 28 to 42 days after Dose One.

Data regarding MAEs were obtained from the Kaiser Permanente computerized health care utilization databases for hospitalizations, emergency department visits and clinical visits. MAEs were analyzed individually and within four pre-specified grouped diagnoses: acute respiratory tract events, systemic bacterial

infections, acute gastrointestinal tract events, and rare events potentially related to influenza. For these four pre-specified grouped diagnoses, no significant increase in risk for FluMist recipients was seen in the combined analyses across all utilization settings, doses and age groups. Selected respiratory tract illnesses of special interest (pneumonia, bronchitis, bronchiolitis, and croup) were included in acute respiratory tract events and were not associated with increased risk for FluMist recipients in any protocol-specified analysis. No systemic bacterial infection occurred. In FluMist recipients, an increased risk was not observed for rare events that have been reported with naturally occurring influenza virus infection, including seizures(s), febrile seizures, and epilepsy. No cases of encephalitis, acute idiopathic polyneuritis (Guillain-Barré syndrome), Reye syndrome, or myocarditis were reported in this study.

In this study, there were approximately 1,500 MAE analyses with 14 individual MAE categories associated with significantly increased risk and 21 with significantly decreased risk in FluMist recipients within 42 days of vaccination. Because of the number of analyses performed without adjustment for multiple comparisons, it was expected that some significant outcomes, increased or decreased, would be observed due to chance alone. Of the 14 individual MAEs associated with increased risk, a biological association with FluMist is plausible for six: upper respiratory infection (URI), musculoskeletal pain, asthma, abdominal pain, otitis media with effusion (OME), and adenitis/adenopathy. After additional evaluation [including assessment of the number and types of analyses associated with the increase and the temporal clustering of events (Appendix 1, Summary of Analyses for Study AV019)], a cause and effect relationship could not be excluded for URI, musculoskeletal pain in children 18–35 months of age, and asthma in children 18–35 months of age.

Asthma and wheezing are discussed further in Section 9. In AV019 an increased risk was observed in FluMist recipients 18–35 months of age (RR 4.06, 90% CI: 1.29,17.86) occurring in 16 of 728 FluMist recipients and 2 of 369 placebo recipients. None of the events required hospitalization.

In the final analysis of Study AV019, a significant increase in conjunctivitis events was observed in the 14 Day Summary Period for children 25–48 months of age who received FluMist. In the cumulative age analyses, the attributable risk for children <60 months of age was approximately 0.5% (an increase was not observed in older children/adolescents or adults).

Serious Adverse Events

Serious adverse events occurred at a low rate (<1%) in FluMist and placebo recipients in healthy children 1–17 years of age. No SAEs were reported as related to vaccination in the completed clinical studies.

5.1.1. Safety in Healthy Children by Age

The solicited adverse events are presented by age in healthy children in Tables 16 and 17. The general pattern was similar in various age groups of children including those under and over five years of age, although as age increased, the relative number of participants reporting irritability and fever declined whereas the relative number of participants reporting sore throat and headache increased. Table 18 presents the solicited adverse events following Dose One in FluMist and placebo recipients for healthy children less than 60 months of age and for those 60 months of age and older.

Medication use including antibiotics, analgesics/antipyretics, antihistamines/antitussives/decongestants, and beta agonist/ glucocorticoids, was assessed overall for the entire study group in the 10-day post-vaccination period. After Dose One, only analgesics/antipyretics was significantly increased (21.8% in FluMist vs. 16.5% in placebo recipients). There were no significant increases after Dose Two. Restricting this comparison to those children ≥60 months, there was no significant increase in analgesics/antipyretics after Dose One.

Table 16
Summary of Solicited Events Observed within 10 Days of Dose One for FluMist and Placebo Recipients in Placebo-Control Studies by Age

	Age									
	12–23 Months		24–35 Months		36–47 Months		48–59 Months		60–71 Months	
Number of Participants	FluMist	Placebo	FluMist	Placebo	FluMist	Placebo	FluMist	Placebo	FluMist	Placebo
	423	162	387	176	254	108	235	114	234	101
Event	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**
Any Reactions	335/418 (80.1)	121/161 (75.2)	293/383 (76.5)	113/176 (64.2)	188/252 (74.6)	61/107 (57.0)	148/233 (63.5)	71/114 (62.3)	151/231 (65.4)	62/101 (61.4)
Cough	114/418 (27.3)	47/161 (29.2)	96/383 (25.1)	45/176 (25.6)	74/252 (29.4)	31/107 (29.0)	57/233 (24.5)	31/114 (27.2)	62/231 (26.8)	33/101 (32.7)
Runny Nose/ Nasal Congestion	285/414 (68.8)	83/159 (52.2)	241/368 (65.5)	81/167 (48.5)	142/237 (59.9)	47/101 (46.5)	110/222 (49.5)	52/108 (48.1)	103/214 (48.1)	42/95 (44.2)
Sore Throat	20/418 (4.8)	11/161 (6.8)	32/383 (8.4)	9/176 (5.1)	26/252 (10.3)	2/107 (1.9)	24/233 (10.3)	11/114 (9.6)	29/231 (12.6)	20/101 (19.8)
Irritability	173/418 (41.4)	71/161 (44.1)	122/383 (31.9)	47/176 (26.7)	63/252 (25.0)	20/107 (18.7)	29/233 (12.4)	21/114 (18.4)	45/231 (19.5)	17/101 (16.8)
Headache	20/414 (4.8)	5/159 (3.1)	24/368 (6.5)	2/167 (1.2)	18/237 (7.6)	3/101 (3.0)	19/222 (8.6)	15/108 (13.9)	38/214 (17.8)	11/95 (11.6)
Chills	15/414 (3.6)	9/159 (5.7)	23/368 (6.3)	5/167 (3.0)	7/237 (3.0)	4/101 (4.0)	9/222 (4.1)	3/108 (2.8)	13/214 (6.1)	5/95 (5.3)
Vomiting	37/414 (8.9)	10/159 (6.3)	25/368 (6.8)	9/167 (5.4)	15/237 (6.3)	3/101 (3.0)	12/222 (5.4)	3/108 (2.8)	10/214 (4.7)	3/95 (3.2)
Muscle Aches	15/414 (3.6)	7/159 (4.4)	20/368 (5.4)	3/167 (1.8)	16/237 (6.8)	3/101 (3.0)	15/222 (6.8)	3/108 (2.8)	13/214 (6.1)	4/95 (4.2)
Decreased Activity	67/414 (16.2)	29/159 (18.2)	66/368 (17.9)	20/167 (12.0)	37/237 (15.6)	10/101 (9.9)	38/222 (17.1)	13/108 (12.0)	30/214 (14.0)	12/95 (12.6)
Fever[a]										
Temp 1	81/418 (19.4)	30/161 (18.6)	78/383 (20.4)	24/176 (13.6)	43/252 (17.1)	7/107 (6.5)	29/233(12.4)	9/114 (7.9)	22/231 (9.5)	10/101 (9.9)
Temp 2	16/418 (3.8)	16/161 (9.9)	14/383 (3.7)	4/176 (2.3)	7/252 (2.8)	2/107 (1.9)	4/233 (1.7)	0/114 (0.0)	5/231 (2.2)	2/101 (2.0)
Temp 3	1/418 (0.2)	0/161 (0.0)	0/383 (0.0)	1/176 (0.6)	0/252 (0.0)	0/107 (0.0)	0/233 (0.0)	0/114 (0.0)	0/231 (0.0)	0/101 (0.0)

[a] Fever

Temp 1: Oral >100°F, rectal or aural >100.6°F, or axillary >99.6°F.

Temp 2: Oral >102°F, rectal or aural >102.6°F, or axillary >101.6°F.

Temp 3: Oral >104°F, rectal or aural >104.6°F, or axillary >103.6°F.

Table 17
Summary of Solicited Events Observed within 10 Days of Dose Two for FluMist and Placebo Recipients in Placebo-Control Studies by Age

	Age									
	12–23 Months		24–35 Months		36–47 Months		48–59 Months		60–71 Months	
Number of Participants	**FluMist**	**Placebo**	**FluMist**	**Placebo**	**FluMist**	**Placebo**	**FluMist**	**Placebo**	**FluMist**	**Placebo**
	368	132	329	137	194	83	179	86	163	75
Event	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**
Any Reactions	232/367 (63.2)	91/132 (68.9)	201/328 (61.3)	84/135 (62.2)	126/194 (64.9)	49/83 (59.0)	108/179 (60.3)	40/85 (47.1)	107/161 (66.5)	40/75 (53.3)
Cough	98/367 (26.7)	43/132 (32.6)	96/328 (29.3)	41/135 (30.4)	71/194 (36.6)	26/83 (31.3)	59/179 (33.0)	19/85 (22.4)	62/161 (38.5)	23/75 (30.7)
Runny Nose/ Nasal Congestion	178/367 (48.5)	69/132 (52.3)	157/328 (47.9)	68/135 (50.4)	94/194 (48.5)	35/83 (42.2)	74/179 (41.3)	26/85 (30.6)	74/161 (46.0)	24/75 (32.0)
Sore Throat	11/367 (3.0)	7/132 (5.3)	18/328 (5.5)	4/135 (3.0)	17/194 (8.8)	5/83 (6.0)	8/179 (4.5)	6/85 (7.1)	15/161 (9.3)	12/75 (16.0)
Irritability	93/367 (25.3)	46/132 (34.8)	72/328 (22.0)	23/135 (17.0)	36/194 (18.6)	12/83 (14.5)	20/179 (11.2)	14/85 (16.5)	16/161 (9.9)	7/75 (9.3)
Headache	12/367 (3.3)	3/132 (2.3)	15/328 (4.6)	3/135 (2.2)	12/194 (6.2)	1/83 (1.2)	13/179 (7.3)	8/85 (9.4)	11/161 (6.8)	12/75 (16.0)
Chills	16/367 (4.4)	0/132 (0.0)	13/328 (4.0)	4/135 (3.0)	8/194 (4.1)	3/83 (3.6)	6/179 (3.4)	2/85 (2.4)	4/161 (2.5)	3/75 (4.0)
Vomiting	33/367 (9.0)	5/132 (3.8)	22/328 (6.7)	0/135 (0.0)	10/194 (5.2)	8/83 (9.6)	13/179 (7.3)	2/85 (2.4)	9/161 (5.6)	9/75 (12.0)
Muscle Aches	8/367 (2.2)	0/132 (0.0)	9/328 (2.7)	4/135 (3.0)	6/194 (3.1)	2/83 (2.4)	4/179 (2.2)	1/85 (1.2)	8/161 (5.0)	3/75 (4.0)
Decreased Activity	50/367 (13.6)	20/132 (15.2)	51/328 (15.5)	15/135 (11.1)	32/194 (16.5)	8/83 (9.6)	18/179 (10.1)	9/85 (10.6)	17/161 (10.6)	10/75 (13.3)
Fever[a]										
Temp 1	40/367 (10.9)	23/132 (17.4)	48/328 (14.6)	14/135 (10.4)	20/194 (10.3)	9/83 (10.8)	21/179 (11.7)	5/85 (5.9)	7/161 (4.3)	3/75 (4.0)
Temp 2	11/367 (3.0)	10/132 (7.6)	9/328 (2.7)	5/135 (3.7)	8/194 (4.1)	3/83 (3.6)	2/179 (1.1)	0/85 (0.0)	1/161 (0.6)	1/75 (1.3)
Temp 3	2/367 (0.5)	1/132 (0.8)	1/328 (0.3)	0/135 (0.0)	1/194 (0.5)	2/83 (2.4)	0/179 (0.0)	0/85 (0.0)	0/161 (0.0)	0/75 (0.0)

[a] Fever
Temp 1: Oral >100°F, rectal or aural >100.6°F, or axillary >99.6°F.
Temp 2: Oral >102°F, rectal or aural >102.6°F, or axillary >101.6°F.
Temp 3: Oral >104°F, rectal or aural >104.6°F, or axillary >103.6°F.

Table 18
Summary of Solicited Events Within 10 Days of Dose One for FluMist Recipients <60 Months and ≥60 Months of Age

	<60 Months of Age		≥60 Months of Age	
	FluMist	**Placebo**	**FluMist**	**Placebo**
Number Vaccinated	1299	560	234	101
Number Returning Diary Cards	1286	558	231	101
Event	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**
Any Reactions	964/1286 (75.0)	366/558 (65.6)	151/ 231 (65.4)	62/101 (61.4)
Cough	341/1286 (26.5)	154/558 (27.6)	62/ 231 (26.8)	33/101 (32.7)
Runny Nose/Nasal Congestion	778/1241 (62.7)	263/535 (49.2)	103/ 214 (48.1)	42/95 (44.2)
Sore Throat	102/1286 (7.9)	33/558 (5.9)	29/231 (12.6)	20/101 (19.8)
Irritability	387/1286 (30.1)	159/558 (28.5)	45/231 (19.5)	17/101 (16.8)
Headache	81/1241 (6.5)	25/535 (4.7)	38/214 (17.8)	11/95 (11.6)
Chills	54/1241 (4.4)	21/535 (3.9)	13/214 (6.1)	5/95 (5.3)
Vomiting	89/1241 (7.2)	25/535 (4.7)	10/214 (4.7)	3/95 (3.2)
Muscle Aches	66/1241 (5.3)	16/535 (3.0)	13/214 (6.1)	4/95 (4.2)
Decreased Activity	208/1241 (16.8)	72/535 (13.5)	30/214 (14.0)	12/95 (12.6)
Fever[a]				
Temp 1	231/1286 (18.0)	70/558 (12.5)	22/231 (9.5)	10/101 (9.9)
Temp 2	41/1286 (3.2)	22/558 (3.9)	5/231 (2.2)	2/101 (2.0)
Temp 3	1/1286 (0.1)	1/558 (0.2)	0/231 (0.0)	0/101 (0.0)

[a] Fever
Temp 1: Oral >100°F, rectal or aural >100.6°F, or axillary >99.6°F.
Temp 2: Oral >102°F, rectal or aural >102.6°F, or axillary >101.6°F.
Temp 3: Oral >104°F, rectal or aural >104.6°F, or axillary >103.6°F.

5.2. Safety in Healthy Adults

Solicited Adverse Events in Healthy Adults

In the five placebo-controlled studies (AV001, AV003, AV004, AV005, and AV009) in healthy adults 18–64 years of age combined, cough, runny nose, sore throat, headache, chills, muscle aches, and tired/weak were reported more often in vaccinated adults than in placebo recipients during the seven days after a single dose (Table 19). The largest absolute differences observed between FluMist and placebo recipients reporting any individual event following a single dose was 16.6% for runny nose, 9.3% for sore throat, and 3.9% for tired/weak (Table 19). Fever >100°F was similar in FluMist and placebo recipients after a single dose (1.3% vs. 1.5%, respectively).

Table 19
Summary of Solicited Events Observed within 7 Days after Dosing for FluMist and Placebo Recipients in Placebo-Controlled Trials; Healthy Adults 18–64 Years of Age

Event	FluMist		Placebo	
	n/N	%	n/N	%
Any event	2232/3208	69.6	965/1589	60.7
Cough	426/3208	13.3	167/1589	10.5
Runny nose	1399/3208	43.6	429/1589	27.0
Sore throat	827/3208	25.8	262/1589	16.5
Headache	1165/2960	39.4	548/1476	37.1
Chills	258/3208	8.0	95/1589	6.0
Muscle aches	503/3208	15.7	228/1589	14.3
Tired/Weak	724/2960	24.5	304/1476	20.6
Fever				
Temp >100°F	42/3208	1.3	24/1589	1.5
Temp >102°F	3/3208	0.1	2/1589	0.1
Temp >104°F	0/3208	0.0	0/1589	0.0

In Study AV009, medication use including antibiotics, analgesics/antipyretics, antihistamines/antitussives/decongestants, and beta agonist/glucocorticoids was assessed in the 7-day post-vaccination period. There were no significant increases in use of these medications by vaccinees compared to placebo recipients.

Other Adverse Events in Healthy Adults

In addition to the solicited events obtained during the first 7 days after immunization, participants also reported other adverse events that occurred during the course of the clinical trials.

For adults 18–64 years of age, headache (1.8% FluMist vs. 1.3% placebo), nasal congestion (8.5% vs. 2.0%), rhinitis (6.6% vs. 3.6%), and sinusitis (3.8% vs 1.9%) occurred in 1% or greater of FluMist recipients and at a higher rate for FluMist compared to placebo recipients.

Serious Adverse Events in Healthy Adults

Serious adverse events occurred at a low rate (< 1%) in FluMist and placebo recipients in healthy adults 18–64 years of age. No SAEs were reported as related to vaccination in the completed clinical studies.

5.2.1. Safety in Healthy Adults by Age

Solicited Adverse Events in Healthy Adults by Age

Table 20 presents the solicited adverse events within 7 days of vaccination by three age categories, 18–34, 35–49, and 50–64 years of age, for healthy adults in Study AV009 by treatment group. Across the eight solicited events (runny nose, cough, sore throat, headache, chills, muscle aches, tired/weak, and fever) the event rate differences between vaccine and placebo recipients were similar for those 50–64 years of age, 35–49 years of age, and 18–34 years of age.

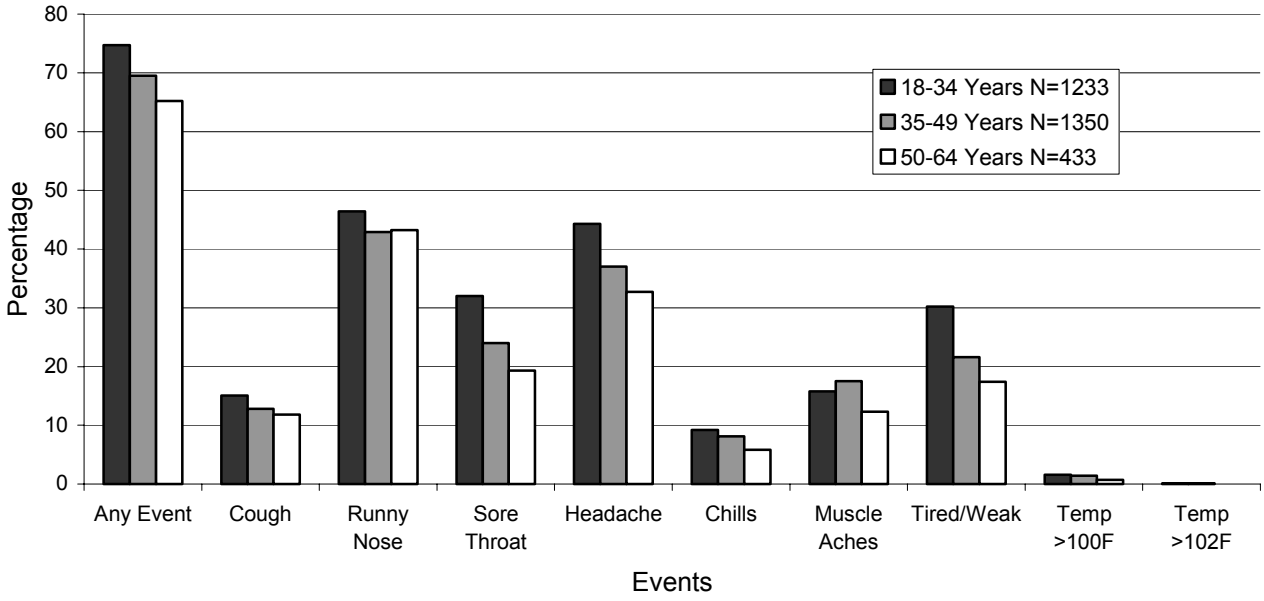
Figure 1 presents the solicited adverse events for FluMist recipients in the three age categories in Study AV009. In general, the pattern of reactogenicity is similar with less events in healthy adults 50–64 years of age compared to younger adults.

Table 20
Reactogenicity Events (Days 0–7) in Healthy Adults 18–64 Years of Age in Study AV009 by Age and Treatment Group

	Age					
	18–34 years		35–49 years		50–64 years	
Number of Participants	**FluMist**	**Placebo**	**FluMist**	**Placebo**	**FluMist**	**Placebo**
Vaccinated	1233	603	1350	705	433	198
Event	**n/N (%)[a]**	**n/N (%)[a]**	**n/N (%)[a]**	**n/N (%)[a]**	**n/N (%)[a]**	**n/N (%)[a]**
Any event	896/1200 (74.7)	367/585 (62.7)	923/1329 (69.5)	432/695 (62.2)	281/431 (65.2)	109/196 (55.6)
Cough	181/1200 (15.1)	65/585 (11.1)	170/1329 (12.8)	71/695 (10.2)	51/431 (11.8)	12/196 (6.1)
Runny nose	557/1200 (46.4)	169/585 (28.9)	570/1329 (42.9)	177/695 (25.5)	186/431 (43.2)	48/196 (24.5)
Sore throat	384/1200 (32.0)	108/585 (18.5)	319/1329 (24.0)	109/695 (15.7)	83/431 (19.3)	22/196 (11.2)
Headache	532/1200 (44.3)	237/585 (40.5)	492/1329 (37.0)	253/695 (36.4)	141/431 (32.7)	58/196 (29.6)
Chills	110/1200 (9.2)	31/585 (5.3)	108/1329 (8.1)	45/695 (6.5)	25/431 (5.8)	14/196 (7.1)
Muscle aches	189/1200 (15.8)	84/585 (14.4)	232/1329 (17.5)	103/695 (14.8)	53/431 (12.3)	28/196 (14.3)
Tired/weak	362/1200 (30.2)	138/585 (23.6)	287/1329 (21.6)	138/695 (19.9)	75/431 (17.4)	28/196 (14.3)
Fever						
Temp >100°F	19/1200 (1.6)	11/585 (1.9)	18/1329 (1.4)	6/695 (0.9)	3/431 (0.7)	3/196 (1.5)
Temp >102°F	1/1200 (0.1)	1/585 (0.2)	1/1329 (0.1)	1/695 (0.1)	0/431 (0.0)	0/196 (0.0)
Temp >104°F	0/1200 (0.0)	0/585 (0.0)	0/1329 (0.0)	0/695 (0.0)	0/431 (0.0)	0/196 (0.0)

[a] Percent calculated on number of participants with diary data available.

Figure 1
Reactogenicity Events (Days 0–7) in Healthy Adults 18 – 64 Years of Age Who Received FluMist in Study AV009 by Age



Other Adverse Events in Healthy Adults by Age Group

Table 21 presents the unsolicited adverse events occurring at a rate of 0.5% or greater within 7 days of vaccination by three age categories, 18–34, 35–49, and 50–64 years of age for healthy adults in Study AV009 by treatment group. Across the adverse events for the individual body systems, the pattern of event rates were similar for FluMist recipients 50–64 years of age to those 35–49, and 18–34 years of age with the differences between treatment groups less for the older age category.

Table 21
(1 of 2)
Adverse Events Days 0–7 in Healthy Adults 18 – 64 Years of Age
in Study AV009 by Age

Number of Participants Randomized	18 – 34 Years of Age		35 – 49 Years of Age		50 – 64 Years of Age	
	FluMist N=1233	**Placebo** N=603	**FluMist** N=1350	**Placebo** N=705	**FluMist** N=433	**Placebo** N=198
Reporting Any Adverse Events	377(30.6)	151(25.0)	422(31.3)	135(19.1)	108(24.9)	32(16.2)
Adverse Event[a]	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**
Body as a whole	**70(5.7)**	**37(6.1)**	**82(6.1)**	**35(5.0)**	**14(3.2)**	**6(3.0)**
Allergic reaction	9(0.7)	4(0.7)	12(0.9)	4(0.6)	2(0.5)	0(0.0)
Headache	4(0.3)	3(0.5)	2(0.1)	0(0.0)	1(0.2)	1(0.5)
Infection	2(0.2)	1(0.2)	0(0.0)	0(0.0)	2(0.5)	0(0.0)
Injury accidental	6(0.5)	3(0.5)	8(0.6)	3(0.4)	2(0.5)	0(0.0)
Malaise	4(0.3)	2(0.3)	11(0.8)	1(0.1)	1(0.2)	0(0.0)
Pain	10(0.8)	1(0.2)	8(0.6)	6(0.9)	3(0.7)	2(1.0)
Pain abdominal	10(0.8)	8(1.3)	7(0.5)	7(1.0)	3(0.7)	3(1.5)
Pain back	11(0.9)	9(1.5)	6(0.4)	8(1.1)	0(0.0)	0(0.0)
Pain neck	3(0.2)	4(0.7)	17(1.3)	1(0.1)	1(0.2)	0(0.0)
Cardiovascular	**6(0.5)**	**2(0.3)**	**7(0.5)**	**4(0.6)**	**3(0.7)**	**1(0.5)**
Vasodilation	3(0.2)	1(0.2)	2(0.1)	1(0.1)	2(0.5)	1(0.5)
Digestive	**78(6.3)**	**49(8.1)**	**68(5.0)**	**32(4.5)**	**22(5.1)**	**10(5.1)**
Diarrhea	29(2.4)	19(3.2)	29(2.1)	12(1.7)	8(1.8)	4 2.0)
Dyspepsia	19(1.5)	14(2.3)	13(1.0)	6(0.9)	8(1.8)	4 (2.0)
Flatulus	0(0.0)	0(0.0)	2(0.1)	0(0.0)	0(0.0)	1(0.5)
Nausea	25(2.0)	16(2.7)	19(1.4)	13(1.8)	6(1.4)	0(0.0)
Ulcer mouth	4(0.3)	3(0.5)	2(0.1)	4(0.6)	0(0.0)	1(0.5)
Vomiting	6(0.5)	3(0.5)	5(0.4)	1(0.1)	0(0.0)	1(0.5)
Hemic and lymphatic	**4(0.3)**	**2(0.3)**	**7(0.5)**	**1(0.1)**	**3(0.7)**	**1(0.5)**
Lymphadenopathy	4(0.3)	2(0.3)	7(0.5)	1(0.1)	3(0.7)	1(0.5)
Musculoskeletal	**9(0.7)**	**6(1.0)**	**16(1.2)**	**6(0.9)**	**5(1.2)**	**4(2.0)**
Arthralgia	6(0.5)	3(0.5)	8(0.6)	3(0.4)	5(1.2)	3(1.5)
Arthritis	0(0.0)	0(0.0)	1(0.1)	0(0.0)	0(0.0)	1(0.5)
Myalgia	2(0.2)	3(0.5)	5(0.4)	1(0.1)	0(0.0)	0(0.0)
Nervous	**23(1.9)**	**16(2.7)**	**30(2.2)**	**14(2.0)**	**7(1.6)**	**5(2.5)**
Dizziness	13(1.1)	6(1.0)	12(0.9)	9(1.3)	0(0.0)	1(0.5)
Dry mouth	3(0.2)	2(0.3)	3(0.2)	3(0.4)	4(0.9)	1(0.5)
Hypertonia	0(0.0)	0(0.0)	2(0.1)	1(0.1)	0(0.0)	1(0.5)
Insomnia	3(0.2)	1(0.2)	2(0.1)	0(0.0)	1(0.2)	1(0.5)
Paresthesia	1(0.1)	2(0.3)	4(0.3)	0(0.0)	2(0.5)	0(0.0)
Tremor	0(0.0)	0(0.0)	0(0.0)	2(0.3)	0(0.0)	1(0.5)

Note: Includes events occurring at a rate of 0.5% or greater, regardless of treatment group.

[a] Presented by Body System and modified COSTART Term.

Table 21
(2 of 2)
Adverse Days 0–7 in Healthy Adults 18 – 64 Years of Age
in Study AV009 by Age

Number of Participants Randomized	18 – 34 Years of Age		35 – 49 Years of Age		50 – 64 Years of Age	
	FluMist N=1233	**Placebo** N=603	**FluMist** N=1350	**Placebo** N=705	**FluMist** N=433	**Placebo** N=198
Reporting Any Adverse Events	377(30.6)	151(25.0)	422(31.3)	135(19.1)	108(24.9)	32(16.2)
Adverse Event[a]	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**	**n(%)**
Respiratory	**216(17.5)**	**46(7.6)**	**263(19.5)**	**56(7.9)**	**67(15.5)**	**9(4.5)**
Bronchitis	11(0.9)	3(0.5)	13(1.0)	5(0.7)	3(0.7)	2(1.0)
Congestion nasal	112(9.1)	15(2.5)	126(9.3)	14(2.0)	36(8.3)	4(2.0)
Epistaxis	6(0.5)	1(0.2)	2(0.1)	1(0.1)	1(0.2)	0(0.0)
Laryngitis	2(0.2)	1(0.2)	3(0.2)	2(0.3)	3(0.7)	0(0.0)
Pharyngitis	6(0.5)	3(0.5)	14(1.0)	2(0.3)	3(0.7)	0(0.0)
Rhinitis	63(5.1)	17(2.8)	99(7.3)	24(3.4)	21(4.8)	5(2.5)
Sinusitis	49(4.0)	14(2.3)	57(4.2)	15(2.1)	16(3.7)	2(1.0)
Skin	**12(1.0)**	**3(0.5)**	**9(0.7)**	**2(0.3)**	**4(0.9)**	**4(2.0)**
Sweat	3(0.2)	1(0.2)	1(0.1)	1(0.1)	2(0.5)	2(1.0)
Ulcer skin	1(0.1)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	1(0.5)
Urticaria	1(0.1)	0(0.0)	1(0.1)	0(0.0)	1(0.2)	1(0.5)
Special Senses	**22(1.8)**	**10(1.7)**	**36(2.7)**	**7(1.0)**	**5(1.2)**	**2(1.0)**
Conjunctivitis	1(0.1)	3(0.5)	3(0.2)	2(0.3)	1(0.2)	0(0.0)
Eye disorder	6(0.5)	2(0.3)	16(1.2)	2(0.3)	0(0.0)	1(0.5)
Pain ear	10(0.8)	1(0.2)	10(0.7)	1(0.1)	3(0.7)	0(0.0)
Tinnitus	1(0.1)	0(0.0)	1(0.1)	0(0.0)	0(0.0)	1(0.5)
Urogenital	**19(1.5)**	**9(1.5)**	**17(1.3)**	**10(1.4)**	**0(0.0)**	**0(0.0)**
Dysmenorrhea	15(1.2)	6(1.0)	16(1.2)	10(1.4)	0(0.0)	0(0.0)
Endometrial disorder	0(0.0)	1(0.2)	0(0.0)	0(0.0)	0(0.0)	0(0.0)

Note: Includes events occurring at a rate of 0.5% or greater, regardless of treatment group.

[a] Presented by Body System and modified COSTART Term.

Serious Adverse Events in Healthy Adults by Age Group

Serious adverse events (SAEs) occurred at a low rate (<1%) in FluMist and placebo recipients in Study AV009. No SAEs were considered vaccine related by the study investigators. There were no cardiac, stroke, or encephalitis events. There was one event of optic neuritis due to cat scratch disease in a FluMist recipient 57 years of age that occurred 50 days after dosing and one pre-existing undiagnosed neuropathy in a 30 year old FluMist recipient. There were three SAEs in FluMist recipients involving the pulmonary system; one hospitalization for chronic bronchitis and asthma in a 65 year old on Day 110, one hospitalization for bronchitis in a 39 year old in the 28 days following vaccination (who refused access to her medical records for documentation), and a hospitalization for acute tracheobronchitis in a 30 year old on Day 36.

5.3. Summary of General Safety in Adults and Children

The safety of FluMist has been studied in 10,321 children/adolescents 60 months through 17 years of age and 3,833 adults 18 through 64 years of age. Overall, reactogenicity to FluMist was low, with runny nose/nasal congestion being reported as the most common FluMist attributable event. Age specific differences were observed, with low grade fever reported more commonly in young children (<60 months) and sore throat and headache more commonly reported in older individuals. When studied, adverse events rates were higher after Dose One compared to Dose Two. In healthy individuals 60 months through 64 years of age, only small increases in adverse events were observed following vaccination.

In children 12–59 months in placebo controlled studies, the most common solicited adverse events after Dose One that were >1% higher in the FluMist group were associated with URI symptoms (i.e., runny nose/nasal congestion, 62.7% vs. 49.2%). Among non-specific events, low grade fever (18.0% vs. 12.5%), irritability (30.1% vs. 28.5%), vomiting (7.2% vs. 4.7%), muscle aches (5.3% vs. 3.0%), and decreased activity (16.8% vs. 13.5%) were higher in the FluMist group. When medication use was evaluated (Dose One), only analgesics/antipyretics was significantly increased (21.8% FluMist vs. 16.5% placebo). In children 12–59 months in AV019, a cause and effect relationship

could not be excluded for the following medically attended events: URI, conjunctivitis, musculoskeletal pain, and asthma/wheezing.

Among children 60–71 months in placebo-controlled trials, solicited events >1% higher in the FluMist group following Dose One included runny nose/nasal congestion (48.1% vs. 44.2%), irritability (19.5% vs. 16.8%), headache (17.8% vs 11.6%), vomiting (4.7% vs. 3.2%), muscle aches (6.1% vs. 4.2%), and decreased activity (14.0% vs. 12.6%). No increase in fever was observed in this age group. No difference in medication use was observed in this older age group.

In placebo-controlled trials in adults 18-64 years of age the following solicited adverse events were reported >1% higher in the FluMist group: cough (13.3% vs. 10.5%), runny nose/nasal congestion (43.6% vs. 27.0%), sore throat (25.8% vs. 16.5%), headache (39.4% vs. 37.1%), chills (8.0% vs. 6.0%), muscle ache (15.7% vs. 14.3%), tired/weak (24.5% vs. 20.6%). No increase in fever was observed among 18–64 year olds.

Serious adverse events following vaccination were uncommon (< 1%) in all age groups and no vaccine related serious adverse events were reported in the proposed population.

6. OVERVIEW OF REVACCINATION

6.1. Safety of Annual Administration of FluMist

Annual dosing with FluMist over three study seasons in healthy children initially 15 to 71 months of age (Studies AV006 Year One, AV006 Year Two and AV015) and over two study seasons in healthy children and adolescents 18 months to 18 years of age in Study AV012 Year One and Year Two support the safety of repetitive dosing. There are no safety data available for re-vaccination with FluMist in healthy adults (18–64 years of age).

In addition to the above data obtained with FluMist, historical annual revaccination data for safety and efficacy of CAIV have been published from several trials (Gruber, Am. J. Dis. Child. 1990; Clover, J. Infect. Dis. 1991; Piedra, Sem. Ped. Inf. Dis. 1991; Edwards, J. Infect. Dis. 1994; Neuzil, Pediatr. Infect. Dis. J. 2001). The largest was a randomized, double-blind, placebo-controlled trial conducted in 5,210 participants over four study seasons with a cold-adapted, live, attenuated, bivalent, type A formulation made with the same master donor type A virus strain derived by Dr. Maassab of the University of Michigan as used for FluMist (Edwards 1994). Four thousand, six hundred twenty of the 5,210 (88.7%) participants in this trial were over ten years of age and most (85%) were over 16 years of age. The cold-adapted vaccine was also compared to the licensed, inactivated vaccine and both vaccines were reported to be safe and effective across the four study seasons (Edwards, J. Infect. Dis. 1994).

6.1.1. Second Year Re-Vaccination in Children in Study AV006

Study AV006 was designed as a two year trial (AV006 Year One and AV006 Year Two) without re-randomization in Year Two. In Year One, 1,314 of 1,602 children were enrolled into a two-dose regimen and randomized to vaccine or placebo; the remaining 288 were enrolled into a one-dose regimen and randomized to vaccine or placebo. Of the 1,070 FluMist and 532 placebo recipients enrolled in Study AV006 Year One, 917 (86%) FluMist and 441 (83%) placebo recipients returned for the second year of the study.

Among those who participated in both years of the study, rates of reactogenicity events in FluMist recipients in Year Two were generally lower than following a

primary dose or series in Year One (Table 22). The proportion of FluMist recipients reporting any reactogenicity event following one and two doses in Year One decreased from 73.5% and 68.5%, respectively, to 57.8% following re-vaccination in Year Two. The most frequently occurring event in Year One, runny nose/nasal congestion, decreased from 58.0% and 50.9% following the first and second dose, respectively, to 42.1% for FluMist participants in Year Two; a similar decrease was seen in placebo recipients.

Table 22
Reactogenicity Events (Days 0–10) in Healthy Children Receiving at Least One Dose of FluMist or Placebo in Two Consecutive Years

	AV006 Year One				AV006 Year Two	
	Post-Dose One		Post-Dose Two		Single Dose	
Number of Participants	**FluMist**	**Placebo**	**FluMist**	**Placebo**	**FluMist**	**Placebo**
Vaccinated	917	441	748	362	917	441
With Diary Data Available	908	439	744	360	912	441
Event	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any event	667 (73.5)	282 (64.2)	510 (68.5)	226 (62.8)	527 (57.8)	254 (57.6)
Cough	248 (27.3)	120 (27.3)	264 (35.5)	123 (34.2)	219 (24.0)	112 (25.4)
Runny nose/Nasal congestion	527 (58.0)	201 (45.8)	379 (50.9)	166 (46.1)	384 (42.1)	186 (42.2)
Sore throat	85 (9.4)	30 (6.8)	45 (6.0)	25 (6.9)	92 (10.1)	37 (8.4)
Irritability	224 (24.7)	104 (23.7)	123 (16.5)	66 (18.3)	132 (14.5)	70 (15.9)
Headache	73 (8.0)	28 (6.4)	38 (5.1)	20 (5.6)	84 (9.2)	31 (7.0)
Chills	28 (3.1)	12 (2.7)	22 (3.0)	9 (2.5)	31 (3.4)	13 (2.9)
Vomiting	46 (5.1)	14 (3.2)	55 (7.4)	17 (4.7)	44 (4.8)	18 (4.1)
Muscle aches	41 (4.5)	12 (2.7)	22 (3.0)	6 (1.7)	26 (2.9)	16 (3.6)
Decreased activity	137 (15.1)	51 (11.6)	90 (12.1)	40 (11.1)	104 (11.4)	56 (12.7)
Fever[a]						
Temp 1	135 (14.9)	50 (11.4)	78 (10.5)	36 (10.0)	99 (10.9)	42 (9.5)
Temp 2	19 (2.1)	11 (2.5)	16 (2.2)	12 (3.3)	26 (2.9)	8 (1.8)
Temp 3	1 (0.1)	1 (0.2)	1 (0.1)	1 (0.3)	2 (0.2)	0 (0.0)

[a] Fever
Temp 1: Oral >100°F, rectal or aural >100.6°F, or axillary >99.6°F.
Temp 2: Oral >102°F, rectal or aural >102.6°F, or axillary >101.6°F.
Temp 3: Oral >104°F, rectal or aural >104.6°F, or axillary >103.6°F.

Excluding reactogenicity events with onset during the first ten days following vaccination in Study AV006 Year Two, 13.5% of FluMist and 14.5% of placebo recipients experienced one or more adverse events (Table 23). Overall rates and absolute rate differences were similar in Year Two to Dose Two in Year One.

Table 23
Adverse Events (Days 0–10) in Healthy Children Receiving at Least One Dose of FluMist or Placebo in Two Consecutive Years

Adverse Event[a]	AV006 Year One				AV006 Year Two	
	Dose One		Dose Two		Dose One	
	FluMist N=917	Placebo N=441	FluMist N=748	Placebo N=362	FluMist N=917	Placebo N=441
	n (%)	n (%)	N (%)	n (%)	n (%)	n (%)
Any Adverse Event	162 (17.7)	63 (14.3)	100 (13.4)	51 (14.1)	124 (13.5)	64 (14.5)
Body As A Whole	74 (8.1)	27 (6.1)	33 (4.4)	16 (4.4)	60 (6.5)	27 (6.1)
Allergic reaction	10 (1.1)	2 (0.5)	0 (0.0)	0 (0.0)	9 (1.0)	7 (1.6)
Infection	10 (1.1)	3 (0.7)	12 (1.6)	3 (0.8)	5 (0.5)	6 (1.4)
Injury accidental	11 (1.2)	3 (0.7)	3 (0.4)	1 (0.3)	14 (1.5)	4 (0.9)
Pain	23 (2.5)	13 (2.9)	3 (0.4)	3 (0.8)	8 (0.9)	6 (1.4)
Pain abdominal	15 (1.6)	1 (0.2)	7 (0.9)	2 (0.6)	10 (1.1)	3 (0.7)
Digestive	47 (5.1)	17 (3.9)	22 (2.9)	15 (4.1)	22 (2.4)	17 (3.9)
Anorexia	11 (1.2)	3 (0.7)	6 (0.8)	3 (0.8)	2 (0.2)	2 (0.5)
Diarrhea	33 (3.6)	13 (2.9)	15 (2.0)	8 (2.2)	12 (1.3)	11 (2.5)
Special Senses	25 (2.7)	8 (1.8)	34 (4.5)	10 (2.8)	20 (2.2)	12 (2.7)
Otitis Media	14 (1.5)	5 (1.1)	23 (3.1)	6 (1.7)	12 (1.3)	6 (1.4)

Note: Excluding reactogenicity events beginning within 10 days of vaccination. Includes only adverse events occurring in ≥1% of participants in any FluMist group.

[a] Presented by Body Class and modified COSTART Term.

6.1.2. Third Annual Re-vaccination

Safety and tolerability following three consecutive years of annual vaccination was assessed for those children who participated in both years of Study AV006 and were enrolled in Study AV015. A total of 642 children 1–8 years of age at the time of initial dosing in Year One received one or more doses of FluMist in each of three consecutive years

The proportion reporting any reactogenicity event or any specific reactogenicity event was similar in the second and third years (Table 24).

Table 24
Reactogenicity Events (Days 0–10) in Healthy Children 1–8 Years of Age Receiving at Least One Dose of FluMist in Three Consecutive Years

	1st Year (AV006)		2nd Year (AV006)	3rd Year (AV015)
	1st Dose	2nd Dose	One Dose	One Dose
Number of Participants				
Vaccinated	642	555	642	642
With Diary Data Available	640	553	640	641
Event	**n (%)**	**N (%)**	**n (%)**	**n (%)**
Any event	472 (73.8)	381 (68.9)	365 (57.0)	353 (55.1)
Cough	166 (25.9)	195 (35.3)	157 (24.5)	170 (26.5)
Runny nose/Nasal congestion	369 (57.7)	280 (50.6)	261 (40.8)	235 (36.7)
Sore throat	55 (8.6)	34 (6.1)	61 (9.5)	50 (7.8)
Irritability	153 (23.9)	90 (16.3)	90 (14.1)	62 (9.7)
Headache	46 (7.2)	30 (5.4)	55 (8.6)	62 (9.7)
Chills	15 (2.3)	14 (2.5)	19 (3.0)	14 (2.2)
Vomiting	31 (4.8)	43 (7.8)	26 (4.1)	32 (5.0)
Muscle aches	26 (4.1)	16 (2.9)	17 (2.7)	19 (3.0)
Decreased activity	98 (15.3)	64 (11.6)	74 (11.6)	61 (9.5)
Fever[a]				
Temp. 1	98 (15.3)	57 (10.3)	68 (10.6)	54 (8.4)
Temp. 2	15 (2.3)	9 (1.6)	18 (2.8)	8 (1.2)
Temp. 3	1 (0.2)	0 (0.0)	2 (0.3)	0 (0.0)

[a] Fever
Temp 1: oral >100°F, rectal/aural >100.6°F, axillary >99.6°F.
Temp 2: oral >102°F, rectal/aural >102.6°F, axillary >101.6°F.
Temp 3: oral >104°F, rectal/aural >104.6°F, axillary >103.6°F.

In general, adverse events other than reactogenicity events were similar in the second and third years and less frequent compared to the first year (Table 25).

Table 25
Adverse Events (Days 0–10) in Healthy Children Receiving at Least One Dose of FluMist in Three Consecutive Years

Adverse Event[a]	1st Year (AV006)		2nd Year (AV006)	3rd Year (AV015)
	1st Dose	2nd Dose	One Dose	One Dose
	N=642 n (%)	N=555 n (%)	N=642 n (%)	N=642 n (%)
Any Adverse Event	118 (18.4)	76 (13.7)	89 (13.9)	88 (13.7)
Body as a whole	61 (9.5)	24 (4.3)	36 (5.6)	33 (5.1)
Allergic reaction	8 (1.2)	0 (0.0)	6 (0.9)	2 (0.3)
Infection	10 (1.6)	7 (1.3)	1 (0.2)	0 (0.0)
Injury accidental	11 (1.7)	3 (0.5)	12 (1.9)	7 (1.1)
Pain	17 (2.6)	3 (0.5)	6 (0.9)	1 (0.2)
Pain abdominal	11 (1.7)	5 (0.9)	3 (0.5)	14 (2.2)
Digestive	33 (5.1)	20 (3.6)	15 (2.3)	19 (3.0)
Anorexia	9 (1.4)	5 (0.9)	0 (0.0)	2 (0.3)
Diarrhea	24 (3.7)	14 (2.5)	9 (1.4)	10 (1.6)
Respiratory	10 (1.6)	16 (2.9)	21 (3.3)	17 (2.6)
Sneezing	0 (0.0)	0 (0.0)	0 (0.0)	8 (1.2)
Skin	4 (0.6)	5 (0.9)	9 (1.4)	10 (1.6)
Rash	1 (0.2)	3 (0.5)	7 (1.1)	6 (0.9)
Special senses	14 (2.2)	23 (4.1)	15 (2.3)	23 (3.6)
Conjunctivitis	2 (0.3)	5 (0.9)	1 (0.2)	7 (1.1)
Otitis media	7 (1.1)	14 (2.5)	9 (1.4)	10 (1.6)
Pain ear	4 (0.6)	2 (0.4)	4 (0.6)	8 (1.2)

Note: Excluding reactogenicity events beginning within ten days after vaccination. Includes only adverse events occurring in ≥1% of participants in any group.

[a] Presented by Body Class and modified COSTART Term.

6.1.3. Serious Adverse Events – Annual Administration

Four SAEs (three FluMist and one placebo) were reported in Study AV006 Year Two: two (one FluMist and one placebo) occurred within the 42–day reporting period and two others were reported later during the conduct of the study (Table 26). All were unrelated to vaccination.

In Study AV015, there were no SAEs reported within the 42–day reporting period. One SAE was reported 43 days after vaccination with FluMist (iatrogenic response to anesthesia). It was considered unrelated to vaccination as determined by the investigator.

Table 26
Serious Adverse Events Occurring with Annual Administration in Healthy Children 12 to 71 Months of Age

Participant Number	Study	Age/ Gender	Treatment Group	Vaccination Date	SAE Start Date	SAE Stop Date	Days Between Vaccination and Onset	Diagnosis	Related to Vaccine[a]
5505	AV006 Year Two	2Y Female	Placebo	10/23/97	11/8/97	11/10/97	13	Salmonella Enterocolitis	No
5141	AV006 Year Two	4Y Male	FluMist	9/10/97	9/18/97	9/27/97	8	Status Asthmaticus (in participant with a prior history of asthma)	No
5778	AV006 Year Two	4Y Male	FluMist	9/11/97	3/26/98	3/28/98	196	Pneumonia/hypoxia	No
6396	AV006 Year Two	2Y Male	FluMist	10/10/97	3/4/98	3/10/98	145	Posterior fossa tumor, R/O Malignant Hyperthermia[b]	No
5597	AV015	4Y Male	FluMist	12/17/98	1/29/99	1/30/99	43	Iatrogenic Response to Anesthesia	No

[a] Related to vaccine defined as definitely, probably, or possibly related.

[b] This participant died.

6.2. Revaccination in Study AV012 Year Two – Participants 18 Months to 18 Years of Age

Annual revaccination of 2,101 children and adolescents 18 months to 18 years of age with FluMist for a second season occurred in Study AV012, the community protection trial conducted in Temple, Texas by investigators from the Baylor College of Medicine. Of these 2,101 participants, four had serious adverse events (SAEs) none of which were judged to be vaccine related.

There was no significant increase in relative risk of MAARI in the Days 0–14 and Days 0–42 Vaccination Periods compared to the Reference Periods for the 1,054 participants in the Scott and White Health Plan (SWHP) initially 18 months to 18 years of age in Study AV012 Year One who were revaccinated in Year Two (Table 27).

Table 27
Relative Risk of MAARI Events for Days 0–14 and Days 0–42 Post-Vaccination vs. the Reference Period in Revaccinees 18 Months to 18 Years of Age with SWHP Coverage for the Safety Analysis Period Prior to the Greatest Intensity of the Influenza Season – Study AV012 Year Two

Event	Days	Revaccinees, Year Two Data (N=1054)					
		Vaccination Period		Reference Period[a]		Poisson Analysis	
		Events	Rate[b]	Events	Rate[b]	RR[c]	90% CI[c]
MAARI	**0-14**	67	132.6	367	130.5	1.00	0.80-1.24
Acute Otitis Media/Sinusitis	**0-14**	16	31.7	118	42.0	0.73	0.47-1.13
Pneumonia	**0-14**	0	0	10	3.6	NA	NA
Bronchitis	**0-14**	1	2.0	19	6.8	0.28	0.05-1.53
Bronchiolitis	**0-14**	0	0	0	0	NA	NA
Croup	**0-14**	2	4.0	7	2.5	1.6	NA
Asthma/Wheezing	**0-14**	1	2.0	26	9.2	0.22	0.04-1.16
MAARI	**0-42**	180	149.6	254	120.2	1.14	0.96-1.36
Acute Otitis Media/Sinusitis	**0-42**	58	48.2	76	36.0	1.14	0.83-1.55
Pneumonia	**0-42**	2	1.7	8	3.8	0.45	NA
Bronchitis	**0-42**	8	6.6	12	5.7	1.03	0.45-2.33
Bronchiolitis	**0-42**	0	0	0	0	NA	NA
Croup	**0-42**	3	2.5	6	2.8	0.89	NA
Asthma/Wheezing	**0-42**	13	10.8	17	8.0	1.38	0.71-2.68

[a] Time period prior to vaccination and after Day 14 or 42.

[b] Event rates presented are per 1,000 person-months.

[c] The Relative Risk (RR) was considered significantly increased if the lower bound of the 90% Confidence Interval (CI) was 1.00 or greater. RR and CI were adjusted for age group and season. The RR is presented without CI when the model did not converge and this RR is not adjusted for age group or season. Not Applicable (NA) means low rate of events does not allow calculation of RR and/or CI.

6.3. Summary of Revaccination Data

Revaccination safety findings from children in Studies AV006, AV015, and AV012 are consistent with previously published findings in trials of CAIV. Solicited adverse events and other reported adverse events were similar but lower in the second and subsequent years than in the first year of FluMist immunization. No SAEs related to FluMist were reported after revaccination. The results of these studies in children support the safety of annual revaccination with FluMist in adolescents and adults.

7. OVERVIEW OF PNEUMONIA

Across the 20 studies, a total of 117 pneumonia events occurred in the 42 days after vaccination (92 events in 91 FluMist recipients, and 25 events in 25 placebo recipients); 44 (38%) of these events were radiographically diagnosed. Of the 117 pneumonia events, 75 were in randomized (2:1), placebo controlled trials (50 in FluMist recipients, 25 in placebo recipients) and 42 were in non-placebo-controlled trials. The pneumonia events were distributed throughout the six week post-vaccination period for both treatment groups, with no evidence of temporal clustering. Two pneumonia events in two FluMist recipients were associated with hospitalization and reported as SAEs.

Incidence for pneumonia is presented in Table 28 for the 14 randomized, placebo-controlled studies for both the 21 Day and 42 Day post-vaccination periods. Within the 21 days after vaccination, there were 28 pneumonia events after 17,304 FluMist doses (2.24 events per 1000 person-months) and 14 events after 8,477 placebo doses (2.28 events per 1000 person-months). Within the 42 days after vaccination, there were 50 pneumonia events after 17,304 FluMist doses (2.30 events per 1000 person-months) and 25 events after 8,477 placebo doses (2.35 events per 1000 person-months).

In the three pivotal studies (AV006, AV009, and AV019), the incidence rates per 1000 person-months in the 21 days after vaccination for FluMist and placebo recipients were 2.30 and 2.50, respectively (Table 28). In the 42 days after vaccination, the incidence rates were 2.38 and 2.56, respectively.

Table 28
Incidence Rates in Randomized, Placebo-Controlled Studies for Pneumonia

Event	Incidence (per 1000 person-months)							
	21 Day Summary Period				28/42 Day Summary Period			
	14 Studies[a]		3 Studies[b]		14 Studies[a]		3 Studies[b]	
	FluMist	Placebo	FluMist	Placebo	FluMist	Placebo	FluMist	Placebo
Pneumonia	2.24	2.28	2.30	2.50	2.30	2.35	2.38	2.56

Note: NA = not available; relative risk point estimates for most analyses of this event could not be computed (i.e, were infinite) due to 0 events occurring in placebo recipients.

[a] The 14 randomized, placebo-controlled studies.

[b] The 3 pivotal randomized, placebo-controlled studies (AV006, AV009, AV019).

In the three large, pivotal, randomized, placebo-controlled studies that evaluated the safety of FluMist, pneumonia events were not associated with a statistically significant increased risk for FluMist recipients. In a large, non-placebo-controlled study, AV012, rates of pneumonia in FluMist recipients in each of two years (0.59–3.96 events per 1000 person months) were similar to rates of pneumonia in FluMist recipients in placebo-controlled trials (Table 28). In addition, analyses within each study year in Study AV012 revealed no increase in pneumonia events in the Vaccination Periods relative to the Reference periods (relative risk for the 42 Day post-vaccination period = 0.77 [90% CI: 0.46, 1.29] and 0.75 [90% CI not able to be calculated due to low event rate] for Year One and Year Two, respectively).

In summary, evidence within and across clinical studies in healthy children and healthy adults indicates that FluMist administration was not associated with an increase risk of pneumonia.

8. CONCURRENT ADMINISTRATION WITH OTHER VACCINES

The safety and immunogenicity of FluMist when administered concurrently with other vaccines have not been evaluated, nor has the degree to which FluMist may affect the safety and immunogenicity of other vaccines when administered concurrently with FluMist. Therefore, FluMist should not be administered concurrently with other vaccines. Clinical studies of FluMist in healthy individuals excluded subjects who received any live virus vaccine within one month of enrollment and any inactivated or subunit vaccine within two weeks of enrollment; therefore, health care providers should adhere to these intervals when administering FluMist until further data can be provided.

MedImmune Vaccines, Inc. has implemented one study to address concurrent vaccination in children in their second year of life. Study AV018 has completed enrollment of 1,200 children 12–15 months of age to assess the safety and immunogenicity of MMRII® and VARIVAX® given concurrently with FluMist or placebo mist compared to FluMist alone. The design of Study AV018 is presented in Table 29.

Table 29
Treatment Plan for Concurrent Use Study AV018

Group	N=1200		
	Day 0	Day 42	Day 72
1	Placebo Mist MMRII® VARIVAX®	FluMist	FluMist
2	FluMist MMRII® VARIVAX®	FluMist	Placebo Mist
3	FluMist	FluMist	MMRII® VARIVAX®

This study enrolled children over two study seasons in both the southern and northern hemispheres. The data for this study are expected to be available by the end of 2003.

Additional studies have been designed to assess the safety and immunogenicity of booster doses of Haemophilus influenzae Type B conjugate vaccine (Hib), Acellular Pertussis Vaccine (DTaP), Inactivated Polio Vaccine (IPV), and Prevnar (7-Valent Pneumococcal Conjugate Vaccine) given concurrently with FluMist or placebo mist compared to FluMist alone in children 12–18 months of age. The design of these studies is under discussion with CBER.

9. OVERVIEW OF ASTHMA AND WHEEZING

In multiple retrospective analyses conducted across studies, no significant increase in risk of asthma/Reactive Airways Disease (RAD)/wheezing/Shortness of Breath (SOB) or asthma/RAD was found in the by-study analyses that evaluated event rates across the general study population (e.g., all participants 15 to 71 months of age in Study AV006, and all participants 1 to <9 years or 9 to 17 years of age in Study AV019). In an initial pre-specified analysis of Study AV019, in which rates of medically attended illnesses were evaluated in subsets of children 1 to <9 years of age, the risk of asthma was significantly increased in FluMist recipients 18 to 35 months of age. These data were presented to VRBPAC in July 2001. Post-hoc analyses, performed to identify more precisely the age-related risk accounting for this observation, evaluated cumulative age cohorts beginning at 12 months of age and increasing by 6 month increments. Using this approach, the relative risk of asthma was shown to peak and achieve statistical significance in the 12 to 53 months of age cohort for both doses combined.

The analytic approach was further refined in this report and applied across both placebo-controlled studies that enrolled large numbers of children, Study AV006 and Study AV019. Rates of both asthma/RAD/wheezing/SOB (a more inclusive analysis given the overlap in coding these four terms) and asthma/RAD were evaluated and presented by dose. Analyses were conducted for all participants and for two subpopulations defined as history positive and history negative for asthma/RAD/wheezing based on historical information in records for Study AV006 and, for Study AV019, based on database search.

Using the cumulative approach, statistically significant increased risk in FluMist recipients was observed only for Study AV019 participants and only in one analysis (Table 30). Because over 800 analyses were performed without multiplicity adjustment, it was expected that some significant outcomes, increased or decreased, would be observed due to chance alone.

Table 30
Significant Increases in Risk in FluMist Recipients in Study AV019 in the Cumulative Age Cohort Analyses

Age (months)	Population	Dose	Outcome	Number of Participants		Rates per 1000 Person-Months FluMist/Placebo	Relative Risk (90% CI)
				FluMist n/N	Placebo n/N		
12–59	All Participants	One	Asthma/RAD	14/2032	2/1025	5.92 / 1.68	3.53 (1.10, 15.66)

Notes: CI=confidence interval.

However, in other analyses, even when statistically significant increased risk was not present, a pattern of increasing risk with increasing age through 59 months was observed, followed by a decline in risk as children over 59 months of age were included. From these cumulative data, 59 months of age was a consistent albeit conservative threshold above which the risk for asthma and wheezing outcomes declined. The data indicate that children >59 months of age who received FluMist were not at increased risk of asthma/RAD or asthma/RAD/wheezing/SOB outcomes (Table 31).

Table 31
Risk in FluMist Recipients in Study AV019 in the Cumulative Age Cohort Analyses

Age (months)	Population	Dose	Outcome	Number of Participants		Rates per 1000 Person-Months FluMist/Placebo	Relative Risk (90% CI)
				FluMist n/N	Placebo n/N		
60–107	All Participants	One	Asthma/RAD	9/1759	6/869	4.40/5.92	0.74 (0.31, 1.86)
60–107	All Participants	One	Asthma/RAD Wheezing/SOB	12/1759	10/869	5.87/9.87	0.60 (0.29, 1.23)

Across all studies, a prior positive history for asthma/RAD/wheezing was the single most important predictor of subsequent events, independent of treatment (i.e., receipt of vaccine or placebo). Therefore analysis was performed for those who were history positive and history negative to identify a potential effect of treatment.

In the history positive population, event rates in children 12–59 months of age were relatively higher for both FluMist and placebo recipients (approximately 6–30 events per 1000 person-months) compared with the history negative population (approximately 0–8 events per 1000 person-months) (Table 32), and the rate differences (computed as the event rate in FluMist recipients minus the event rate in placebo recipients) were

relatively larger (approximately 4–8 events per 1000 person-months vs. <3 events per 1000 person-months). In contrast to the history negative population, the history positive population was a relatively small subset (e.g., 27% of Study AV019 participants), and this smaller sample size may account for the inability to detect significantly increased risk when the relative risk point estimates were high. The increases in risk that were observed, however, are biologically plausible in this history positive population. Based on higher event rates, relative risk, and rate differences in the history positive population, and on biologic plausibility for a cause and effect relationship between receipt of FluMist and these outcomes, further analyses and study of the safety of FluMist in individuals with a prior history of asthma, RAD, or wheezing are warranted.

In the history negative population, risk for the asthma/RAD/wheezing/SOB and asthma/RAD outcomes was increased in some analyses of children 12–59 months of age who participated in Study AV019. History negative participants (73% of Study AV019 participants) represented a much larger sample size compared with the history positive participants. In light of this larger sample size, there was a greater likelihood of identifying outcomes associated with statistical significance compared with the history positive population; however, none of the outcomes that were increased in history negative FluMist recipients in this report were statistically significant. Furthermore, rates in history negative participants 12–59 months of age in Study AV019 (approximately 0–8 events per 1000 person-months) were substantially smaller than the corresponding rates in history positive participants, and the magnitude of the rate differences between FluMist and placebo recipients was relatively small (Table 32).

Chart reviews were conducted on Study AV019 participants who were 12 to 53 months of age and who experienced an asthma/RAD/wheezing/SOB outcome in the 42 days post-vaccination. These reviews revealed that the events that occurred, although medically attended, were of low severity. Most events were evaluated and treated in a single outpatient visit, none required hospitalization or referral to a subspecialist for treatment, and standard beta-agonist therapy was most often prescribed. Only approximately 5% of FluMist recipients diagnosed with wheezing/SOB and approximately 20% of FluMist recipients diagnosed with asthma/RAD were treated with oral corticosteroids.

Across both history positive and history negative populations, the asthma/RAD/ wheezing/SOB outcomes that did occur were generally of low severity. Of note, the two study participants who were hospitalized for asthma/RAD (1 FluMist recipient in Study AV006 Year Two, 1 placebo recipient in Study AV002) had a prior history of asthma, and each hospitalization lasted one day.

Significant increased risk in FluMist recipients for asthma/RAD was seen only in Study AV019, but not in Study AV006. The explanation for these different findings is not readily apparent, but some of the differences between the two study designs are important to consider. Study AV019 enrolled approximately 2.4 times as many children in the comparable age group (≤60 months) as were enrolled in the multicenter Study AV006, and therefore had higher power to detect a treatment effect. In addition, because of the number of analyses performed in AV019 (over 800 confidence intervals were generated) without adjustment for multiple comparisons, it was expected that some significant outcomes, increased or decreased, would be observed due to chance alone.

In children 5 to 9 years of age, the incidence rates of asthma/RAD outcomes and asthma/RAD/wheezing/SOB outcomes (Table 33) were generally lower than the corresponding rates in children <5 years of age (Table 32).

Table 32
Summary of Rates of Asthma/RAD/Wheezing/SOB and Asthma/RAD in History Positive and History Negative Study Participants 12–59 Months of Age in Study AV019

Outcome	Dose	History Positive			History Negative		
		Rates per 1000 Person-Months		Rate Difference	Rates per 1000 Person-Months		Rate Difference
		FluMist	Placebo		FluMist	Placebo	
Asthma/RAD/Wheezing/SOB	One	19.98	12.04	7.94	7.01	4.66	2.35
	Two	29.99	25.58	4.41	7.88	8.10	-0.22
Asthma/RAD	One	13.83	6.02	7.81	2.92	0	2.92
	Two	21.00	14.21	6.79	5.07	3.47	1.60

Table 33
Summary of Rates of Asthma/RAD/Wheezing/SOB and Asthma/RAD in History Positive and History Negative Study Participants 5 to 9 Years of Age in Study AV019

Outcome	Dose	History Positive			History Negative		
		Rates per 1000 Person-Months		Rate Difference	Rates per 1000 Person-Months		Rate Difference
		FluMist	Placebo		FluMist	Placebo	
Asthma/RAD/Wheezing/SOB	One	14.88	19.56	-4.68	2.66	6.60	-3.94
	Two	12.20	22.59	-10.39	2.56	2.57	-0.01
Asthma/RAD	One	13.02	11.74	1.28	1.33	3.96	-2.63
	Two	3.49	15.06	-11.57	1.28	2.57	-1.29

Asthma in Adults

In Study AV009, the healthy working adult effectiveness trial, 36 (23 FluMist recipients and 13 placebo recipients) of the 4,561 participants enrolled were determined to have a diagnosis of asthma prior to entry into the trial. Two of 23 FluMist recipients and one of 13 placebo recipients had an asthma exacerbation within the seven days following dosing. None of the exacerbations required hospitalization.

In the retrospective analysis of all asthma/RAD/wheezing/SOB events, there were no significant increases in risk of these events for FluMist recipients 18 to 64 years of age.

Study AV010

Study AV010 was the only study that prospectively evaluated the outcomes of asthma in participants with asthma. This study enrolled 48 children nine to 17 years of age with moderate to severe asthma (consistent with the 1997 guidelines of the National Heart, Lung, and Blood Institute and defined per protocol as forced expiratory volume in one second [FEV1] <80% predicted at baseline and ≥12% increase after bronchodilator treatment). An analysis of this study found no significant difference between the FluMist and placebo groups in mean percent change for percent predicted FEV1 from baseline (Day –7 and Day 0 combined) to the post-vaccination FEV1 (the primary endpoint), and no statistically significant differences for any other measure of asthma stability, including other pulmonary function indices, bronchodilator medication use, clinical asthma symptom scores, and nighttime awakening scores through 28 days post-vaccination. However, two of 24 FluMist recipients (vs. none of 24 placebo recipients) experienced

protocol-defined asthma exacerbations (i.e., increased bronchodilator use or oral corticosteroid use) in the 28 days following vaccination, on Days 2 and 3, respectively. While this difference (2 vs. 0) was not significant, the study was not sufficiently powered to address this endpoint. In the data which analyzed outcomes for 42 days after vaccination, a third asthma/RAD event was included in the FluMist group that occurred 32 days after vaccination (outside the study-defined 28 day period); this difference (3 vs. 0) was not significant (p=0.234, Fisher's exact test).

Conclusions

In this retrospective analysis of the asthma/RAD/wheezing/SOB outcome and the asthma/RAD outcome the following conclusions apply:

- Across all studies, 2 study participants (one FluMist recipient and one placebo recipient) were hospitalized for asthma/RAD: the FluMist recipient in Study AV006 Year Two was hospitalized for status asthmaticus 8 days after receiving a third FluMist dose; the placebo recipient was hospitalized twice for RAD, once 4 days after receiving placebo in Study AV002, and again 33 days later. Both participants had a prior history of asthma, and each hospitalization lasted 1 day.
- No significant increase in risk for either asthma/RAD/wheezing/SOB or asthma/RAD was observed in the general study populations (i.e., FluMist recipients 1 to <9, 9 to 17, and 18 to 64 years of age).
- When children 12 to 107 months of age were examined by cumulative 6 month intervals, a significant increase in risk of asthma/RAD was observed in children <59 months of age in the "All Participants" population in Study AV019. In other analyses, a pattern of increasing relative risk with the incremental inclusion of older children followed by a decline was observed even when risk was not significantly increased, suggesting that an age-related risk for asthma and wheezing outcomes in FluMist recipients may exist.
- An increased risk of asthma/RAD/wheezing/SOB or asthma/RAD was not observed in children ≥59 months of age.
- The inability to detect a significantly increased risk in asthma/RAD/wheezing history positive participants who received FluMist may be due to a combination of background rates of illness from their underlying pulmonary disease, the low number of events overall, and the relatively small proportion of such individuals in

the study. However, the event rates and rate differences were higher than in the history negative participants, and the observed increases in risk are biologically plausible and may represent a true increase in risk.

- The history negative participants represented a population with no known pulmonary disease, or unrecognized disease, and a much larger sample size in which relatively small differences in event rates between treatment groups could more readily reach statistical significance. Although increased risk was observed in some analyses, none were statistically significant. Event rates and rate differences in history negative participants were substantially smaller than in the history positive participants.
- Chart reviews for participants with asthma/RAD and with wheezing/SOB outcomes in Study AV019 indicated that the events that occurred were generally of low severity and responded to standard outpatient medical management. No participants in Study AV019 were hospitalized for treatment of these outcomes.
- The event rates observed in both the history positive and history negative participants in Study AV019 were low and the events were without serious sequelae.
- There were no significant increases of asthma/RAD events for adults 18 to 64 years of age. Of 36 participants with a prior history of asthma in Study AV009, two of 23 FluMist recipients and one of 13 placebo recipients had an asthma exacerbation following dosing; none required hospitalization.
- In Study AV010, 48 children with moderate to severe asthma randomized 1:1 vaccine to placebo showed that FluMist was generally safe and well-tolerated. Two asthma exacerbations in the FluMist group occurring two and three days post-vaccination were treated with standard therapy by the participants; neither required hospitalization.

10. OVERVIEW OF CNS EVENTS

Data on CNS events that may be associated with wild-type influenza infection come primarily from the database driven Studies AV019 and AV012 in children ≤18 years of age and from Study AV009 in adults. CNS events identified were further evaluated by review of medical records to distinguish new or acute events from routine follow-up visits for pre-existing illnesses. Events for which medical records were not able to be found were assumed to be new onset illnesses for purposes of analysis. Overall, no cases of encephalitis, acute idiopathic polyneuritis (Guillain-Barré syndrome), Reye syndrome, or other wild-type influenza-associated rare disorders occurred.

In Study AV019, no significant differences in CNS events occurring within 42 days of vaccination were identified. The CNS event rates were 0.63 events per 1000 person-months in FluMist and 0.48 events 1000 person-months in placebo recipients. All of the identified events were seizures or epilepsy. CNS events occurred in 7 of 6,473 FluMist recipients (0.11%) and 3 of 3,216 placebo recipients (0.09%).

In the placebo controlled trials other than Study AV019, there were two children with seizures: a 39 month old child in Study AV006 (placebo recipient) with no prior history of seizures had a febrile seizure 10 days after her second dose of placebo, and a 31 month old child in Study AV007 (FluMist recipient) with a prior history of reflex seizures had an episode diagnosed as a vasovagal response or reflex seizures 23 days after her second dose of FluMist (Table 34). Overall, six of these eight FluMist recipients and three of the four placebo recipients had a prior history of seizures. In the two large placebo-controlled pediatric trials (AV006 and AV019), only two FluMist recipients and two placebo recipients over five years of age had CNS events post-vaccination.

To compare CNS events between Studies AV019 and AV012, rates within 28 days of vaccination were determined. In Study AV019 during this period, there were six events in 6,473 FluMist recipients for a rate of 0.67 per 1000 person-months and three events in 3,216 placebo recipients for a rate of 0.68 per 1000 person-months. Five of the seven events in FluMist recipients were in children <5 years of age; in participants 5–18 years of age, two events occurred in FluMist recipients and two events occurred in placebo recipients. CNS event rates in Study AV012 Year One and Year Two were similar to those in AV019 (Year One, 0.97 events per 1000 person months and Year Two, 0.88 events per 1000 person months).

Only two participants in Study AV009 (adults), reported CNS events and had no confirmation of a pre-existing diagnosis; one FluMist recipient with confusion and blurred vision on the day of vaccination and one placebo recipient with neck pain, nausea, and delirium two days post-vaccination.

Table 34
Participants with Seizure Events Days 0–42 in Placebo-Controlled Trials

Study Number	Participant Number	Sex	Age (months)	Treatment Dose One	Vaccination One Date	Vaccination Two Date	Date of Event	Event	Days Since Last Vaccination	Prior History of Seizure
AV019	10373	Female	30	FluMist	29-Nov-00	---	14-Dec-00	Seizure(s) Syncope/LOC	15	Yes
AV019	12980	Female	16	FluMist	13-Nov-00	15-Jan-01	12-Dec-00	Seizure, Febrile	29	No
							13-Dec-00	Seizure, Febrile	30	No
AV019	13129	Male	48	Placebo	06-Nov-00	11-Dec-00	28-Dec-00	Seizure, Febrile	17	Yes
AV019	15279	Female	91	FluMist	29-Nov-00	---	22-Dec-00	Seizure, Febrile	23	Yes
AV019	15530	Female	19	FluMist	31-Oct-00	28-Nov-00	17-Nov-00	Seizure, Febrile	17	Yes
AV019	15573	Female	20	FluMist	08-Nov-00	08-Dec-00	29-Dec-00	Seizure, Febrile	21	Yes
AV019	11097	Female	21	FluMist	17-Nov-00	20-Dec-00	12-Dec-00	Epilepsy	25	Yes
AV019	13433	Male	79	Placebo	30-Nov-00	11-Jan-01	08-Jan-01	Epilepsy	39	Yes
AV019	35377	Female	135	Placebo	10-Nov-00	---	11-Dec-00	Epilepsy	31	Yes
AV019	40756	Male	191	FluMist	11-Dec-00	---	28-Dec-00	Epilepsy	17	Yes
AV006	5932	Female	39	Placebo	03-Oct-96	05-Dec-96	15-Dec-96	Febrile Seizure	10	No
AV007	1198	Female	31	FluMist	07-Jul-97	13-Aug-97	05-Sep-97	Convulsion Secondary to Head Injury	23	Yes

Note: This table excludes one participant in Study AV019 (#13142) who received the coded diagnosis "seizure, febrile" in error.

Conclusions:

No statistically significant differences were observed in FluMist recipients with regard to CNS events, primarily seizures, in the two large, controlled studies in children (Study AV006 and Study AV019). Review of all controlled trials did not show any evidence of increased risk of CNS events among FluMist recipients. In all controlled studies, two vaccinees and two placebo recipients older than five years of age had seizures or epilepsy events post-vaccination. No seizures occurred in adults in Study AV009. Across all studies, there were no events of Reye syndrome, Guillain-Barré syndrome, encephalopathy, or new onset encephalopathy.

11. OVERVIEW OF TRANSMISSION

Because FluMist contains live influenza viruses as the active components of the product, it is important to examine the potential for transmission of these viruses from the vaccine recipient to contacts, and to predict the consequences of these transmission events from both the clinical and public health perspectives. This section of the briefing document will present an overview of available data to address the following questions:

- To what extent can the live viruses contained in FluMist be transmitted to contacts?
- Under what epidemiological circumstances would these viruses most likely be transmitted?
- Are any inherent phenotypic or genotypic properties of these viruses changed as a result of transmission?
- Could any unusual or adverse clinical or public health consequences occur as a result?

11.1. Transmissibility of Cold-Adapted Influenza Virus Vaccine (CAIV) Strains

Person-to-person transmission of any vaccine virus requires that vaccinated individual shed vaccine virus in an amount that is equal to or greater than the human infectious dose. Historical shedding data for cold-adapted influenza vaccine (CAIV) in children and adults collected over the past 19 years indicates that the mean peak titer of CAIV shed in nasal secretions of children and adults is generally less than 10^4 and 10^2 $TCID_{50}$, respectively. Historical infectivity data also indicate that the median human infectious dose (HID_{50}) for CAIV in children and adults was generally more than 10^3 and 10^5, respectively (Table 35). Thus, in general, the amount of CAIV shed following vaccination is generally less than the amount of CAIV required to infect exposed individuals. Based on these data, one would predict that CAIV would transmit much less efficiently than wild-type influenza, which is shed in higher titers and is more infectious.

Table 35
Median Human Infectious Dose (HID_{50}) of
CAIV in Serosusceptible Children and Adults

Population	Reference	CAIV Strain	HID_{50} (Log_{10} $TCID_{50}$)
Children		**H1N1**	
	Keitel 1994	A/Hong Kong /123/77	6.0
	Belshe 1984	A/California/10/78	3.5
	Steinhoff 1991	A/Kawasaki/9/86	2.6
		Mean	**4.1**
		H3N2	
	Keitel 1994	A/Washington/897/80	3.5
	Anderson 1989	A/Korea/1/82	4.6
	Steinhoff 1990	A/Bethesda/1/85	4.4
		Mean	**4.2**
		B	
	Anderson 1992	B/Texas/1/84	4.5
	Edwards 1991	B/Ann Arbor/1/86	2.5
		Mean	**3.5**
Adults		**H1N1**	
	Murphy 1980	A/Hong Kong/123/77	5.0
	Murphy 1984	A/California/10/78	6.1
	Keitel 1994	A/Dunedin/1/82	5.3
	Sears 1988	A/Texas/1/85	4.9
		Mean	**5.3**
		H3N2	
	Clements 1983	A/Alaska/6/77	5.5
	Betts 1988	A/Peking/2/79	5.0
	Betts 1988, Clements 1984	A/Washington/897/80	6.0
	Keitel 1994	A/Korea/1/82	5.5
	Sears 1988	A/Bethesda/1/85	6.4
		Mean	**5.7**
		B	
	Keitel 1990	B/Texas/1/84	5.4
	Clements 1990	B/Ann Arbor/1/86	6.4
		Mean	**5.9**

The transmissibility of monovalent and bivalent formulations of CAIV has been examined in healthy children and young adults in studies conducted prior to the development of FluMist. Based on the data presented in Table 35, it could be predicted that it would be more likely for transmission to occur in the pediatric population than among adults. This is because, compared to adults, children are more susceptible to infection by vaccine virus, shed vaccine virus for a longer time and at higher titer, and are more likely to come in contact with respiratory secretions of others. In contrast, adults generally shed lower titers of vaccine virus and are less susceptible to infection with vaccine virus than children.

As shown in Table 36, in ten published studies in which close contacts of monovalent and bivalent CAIV recipients were monitored, there was no evidence of transmission in children, college students and married adults. In a study in which 47 children were vaccinated with monovalent type A CAIV, the level of vaccine virus shedding was lower than the reported HID_{50} of CAIV in children (~$10^{3.5}$ $TCID_{50}$). Likewise, the titer of shed virus in adults is below their HID_{50} which may account for the inability of the investigators to demonstrate vaccine transmission.

Table 36
(1 of 2)
Summary of Historical Transmission Studies

Reference	Strain	Name	Serostatus	Number of Vaccinees	Age	Vaccine Titer (log_{10})[a]	Virus Shedding Peak Mean ± SE (log_{10} titer)	Results
Wright 1982	H3N2 Monovalent	CR29	Seronegative	10	1.5–4.5 Years	6.4	3.5 ± 0.3	None of the 6 placebo controls was infected in spite of close daily contact with vaccinees.
	H1N1 Monovalent	CR35		14	1.5–4.5 Years	6.4	3.6 ± 0.4[b]	
Wright 1986	H3N2 Monovalent	NR	Seronegative	NR	Children	NR	NR	This review article states that no transmission of virus was observed in 15 seronegative placebo recipients in close daily contact with vaccinees in a day care setting.
			Seropositive					
	H1N1 Monovalent	NR	Seronegative					
			Seropositive					
Couch 1986	H1N1 Monovalent	CR35	Serosusceptible	25	College	7.5	NR	Fifty college roommate pairs (100 students) were randomized by pair so that one of the pair received CAIV and the other received placebo. An absence of virus shedding and antibody responses were taken as evidence for lack of transmission in this close contact situation.
			Serosusceptible	25	College	6.5	NR	
Belshe 1984a	H1N1 Monovalent	CR37	Seronegative	47	1–4 Years	3.2–7.2	24/47 shed 3.0 maximum titer	Investigators calculated the HID_{50} to be ~$10^{3.5}$ $TCID_{50}$ and documented that the virus was shed at a lower level than the HID_{50} ($10^{3.5}$ $TCID_{50}$). They concluded that the quantity would be too low to infect other seronegative children.
Clements 1990	B Monovalent	CRB 117	Serosusceptible	32	18–40	7.5	9/32 shed 0.8 ± 0.1 peak titer	Virus recovered from three vaccinees retained the *ts* phenotype. The quantity of virus shed in nine cases was 100,000 times less than the HID_{50} ($10^{6.4}$ $TCID_{50}$) for the reassortant virus (CRB 117), suggesting that it would not be readily transmissible.

[a] All vaccine titers are reported as $TCID_{50}$ unless otherwise noted.

[b] Data are from only those who shed virus.

NR = Not reported.

Table 36
(2 of 2)
Summary of Historical Transmission Studies

Reference	Strain	Name	Serostatus	Number of Vaccinees	Age	Vaccine Titer (log_{10})	Virus Shedding Peak Mean ± SE (log_{10} titer)	Results
Davenport 1977	H3N2 B Bivalent	NR	Serosusceptible and Seropositive	25	19–44 Years	5.8 5.7 (EID_{50})	NR	Spouses of 11 participants who shed virus showed no shedding themselves and no increase in HAI antibody titer was detectable. Spouses of non-shedders also showed no evidence of infection.
Davenport 1971	Type A, Type B	NR	Unscreened	40	10–22 Years	2.7 5.7 (EID_{50})	0/20 shed 5/20 shed	Forty institutionalized patients. No evidence of transmission.
Moritz 1980	H3N2 Monovalent	CR22	Serosusceptible	19	Students	7.8 ($TCID_{50}$)	6/38 shed 1.7 average titer	19 pairs of students were housed as roommates – one of each pair was inoculated with either virus or placebo. None of the placebo group showed any changes in serum antibody titers 17 days after vaccination. No viruses were isolated from the placebo contacts.
Reeve 1980	H1N1 Monovalent	CR33 BG12	Serosusceptible	39	19–26	7.4 – 1st 8.7 – 2nd (EID_{50})	NR	No viruses were isolated from the placebo groups housed in close contact with the vaccinees. There were no revertant viruses observed.
Van Voorthuizen 1981	H1N1 Monovalent	DU 5	2/3 were serosusceptible based on antibody titers	14	19–28	7.4 (EID_{50})	9/14 vaccinees shed None in the Placebo group shed	Vaccine and placebo treated volunteers lived in close association for 10 days. Placebo recipients did not develop serum HAI antibody and virus was not detected in nasal swab specimens. All viral isolates from vaccinees were identical to the vaccine virus, indicating genetic stability.

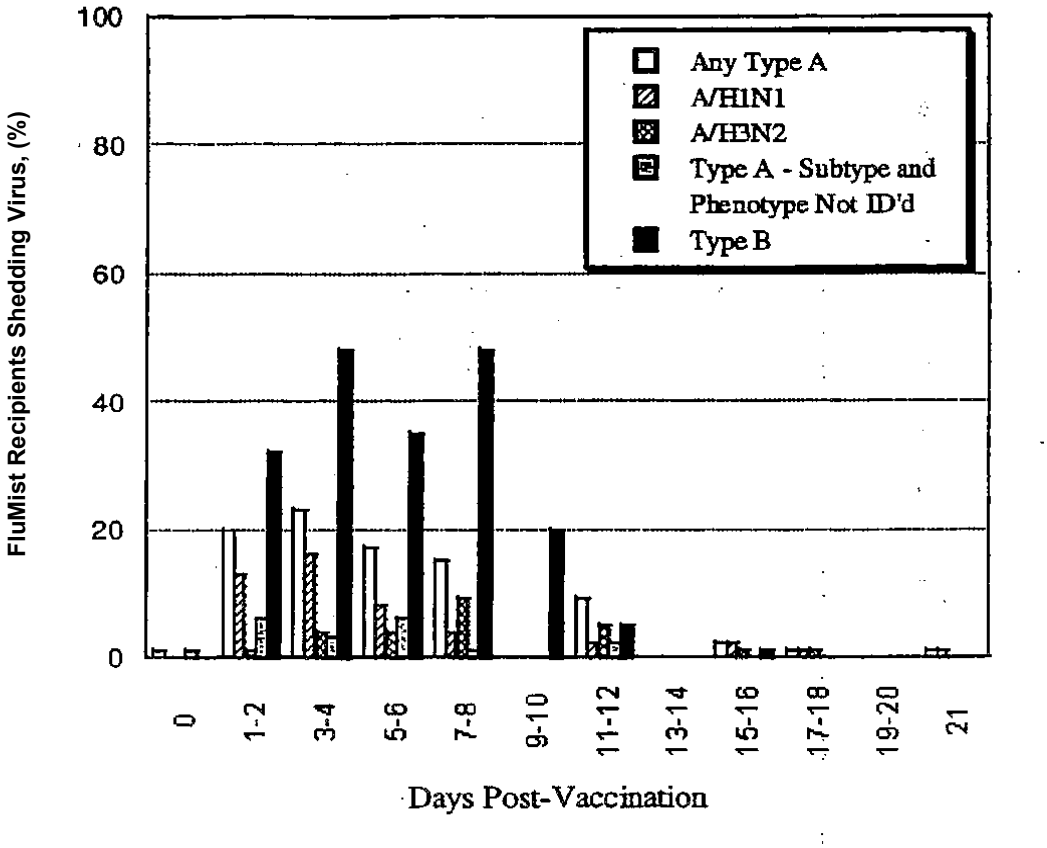
NR = Not reported.

11.2. Transmissibility of FluMist

A prospective, direct assessment of the transmissibility of FluMist was carried out as a randomized, double-blind, placebo-controlled trial in 197 daycare children 8–36 months of age in Finland during November 1999 by Wyeth Lederle Vaccines. The primary objective of the study was to assess whether influenza vaccine is transmitted from vaccinated children to their unvaccinated contacts in a day care setting, and if so, to estimate the rate of transmission. This design was used because young children without prior immunity to influenza virus shed vaccine virus at higher titers and for longer duration than older children or adults and because the daycare environment is known to facilitate transmission of wild-type influenza viruses and other infectious agents. The study was purposefully designed to maximize the potential for transmission and thus could be considered as a "worst case" transmission scenario. This study is one of the largest and most comprehensive of its type, second only to the 1958 landmark study conducted by Gelfand et al (n=281) of the transmission of Sabin-derived oral poliovirus vaccine (OPV). Children enrolled into the FluMist study had to attend daycare at least three days per week/four hours per day and be part of a contact group of at least four children in the playroom with at least one child randomized to vaccine. A total of 197 children were randomized to receive a single intranasal dose of 10^7 $TCID_{50}$ of FluMist (N=98) or placebo (N=99). Virus shedding was examined by culture of nasal swabs prior to dosing and the day after dosing and approximately three times per week for three weeks. There were over 2,000 cultures obtained in the study; approximately 10 cultures from each child (1,027 swabs in 98 vaccinees and 1,036 in 99 placebo recipients).

Eighty percent of FluMist recipients shed at least one vaccine strain, with a mean duration of shedding of 7.6 days. Figure 2 presents the shedding profiles of the three vaccine strains after vaccination in FluMist recipients. The majority of virus shedding occurred between Days 1 and 12 following vaccination with few subjects shedding vaccine virus after Day 12. In all instances, vaccine virus strains shed from FluMist recipients demonstrated preservation of the cold-adapted (*ca*) and temperature-sensitive (*ts*) phenotypes.

Figure 2
Virus Shed by FluMist Recipients in Study D145-P500



Interpretation of the study results in regard to transmission to placebo recipients is complicated by the circulation of confirmed wild-type influenza A/Panama/2007-99-like (H3N2) in the community in Finland and in the study cohort.

Seven placebo recipients shed any influenza virus, that is, wild-type, vaccine type, or unknown type. Table 37 presents a summary of the shedding results for these seven placebo participants. To understand the likelihood of transmission to these placebo participants, it is useful to note that Day 0 cultures were obtained from participants prior to dosing and that there was no co-mingling between daycare playgroups. Forty-nine of the 51 playgroups were located in separate buildings in geographically distinct areas in Tampere or Turku, Finland (Appendix 2, Figure 1). The other two playgroups were located in separate rooms in a single building. No transmission or possible transmission event was detected from these latter two daycare playgroups.

Table 37
Placebo Recipients Shedding Influenza Virus

Participant Number	Day Post-Vaccination	Virus Type Detected[a]	Subtype[b]	Consensus Sequence[c]	Playgroup
1076	1	Type A	H3N2	Wild-type Panama-like	225
	3		H3N2	Wild-type Panama-like	
1090	20	Type A	H3N2	Wild-type Panama-like	107
	21		H3N2	Wild-type Panama-like	
1197	15	Type B	B	Vaccine B/Harbin-like	250
1028	8	Type A	No Result[d]	Not Done	219
1040	0	Type A	No Result[d]	Not Done	205
1026	0	Type A	No Result[d]	Not Done	201
	6	Type A	No Result[d]	Not Done	
1001	15	Type A	No Result[d]	Not Done	101

[a] Virus culture for detection of virus shedding was performed by Turku Laboratory.
[b] Virus subtyping was performed by Aviron Laboratory.
[c] Sequencing was performed by Wyeth Laboratory.
[d] No Result indicates that the virus could not be subtyped because no viable virus could be isolated from the clinical specimen.

The likelihood of transmission to these placebo participants are discussed below and the composition of their playgroups are shown in Appendix 2 (Tables 1–7).

Two placebo recipients shed confirmed wild-type virus; Participant 1076 (Playgroup 225, Appendix 2, Table 1) on Days 1 and 3 post-dosing (January 5 and 7) and Participant 1090 (Playgroup 107, Appendix 2, Table 2) on Days 20 and 21 post-dosing (January 31 and February 1).

Participant 1197 is the single confirmed transmission event; this participant shed vaccine virus type B on Day 15 (March 1) that was identical to the vaccine virus type B shed by a vaccinee (Participant 1204) in the same playgroup four days earlier (Day 8 after dosing on February 25) (Playgroup 250, Appendix 2, Table 3). Additional nasal swab specimens obtained from the participants during scheduled visits on Days 0, 1, 3, 6, 8, 10, 13, 17, 20, and 27 following vaccination were negative for any influenza virus, suggesting that this participant shed low levels of virus for probably one and no more than three consecutive

days. Furthermore, this participant was part of a contact group of five enrolled children, two vaccine and three placebo recipients and both vaccinees shed type B vaccine virus. The safety profile for this child following transmission included: cough on Days 8–10, runny nose Days 8–18, and irritability on Days 14 and 17. All participants (vaccinees and placebo recipients) in the study were offered a dose of FluMist 28–42 days after their initial dose. This participant did receive this optional dose and experienced runny nose on Days 4, 7, and 8 and irritability on Days 5 and 6.

The remaining four placebo recipients shed virus that could not be identified further as wild-type or vaccine virus. Participant 1028 shed type A virus on Day 8 (November 26) (Playgroup 219, Appendix 2, Table 4). One vaccinee (Participant 1021) in this playgroup shed type A vaccine virus 9 and 7 days (November 17 and 19) prior to this placebo recipient shedding. Therefore, this is a possible second transmission event, although it could also be wild-type virus.

Participant 1040 shed type A virus on Day 0 (November 23) (Playgroup 205, Appendix 2, Table 5) which was two days before the single vaccinee in that playgroup (Participant 1048) was vaccinated (November 25). Thus, this culture could not be a transmitted vaccine virus.

Participant 1026 shed type A virus on Days 0 and 6 (November 18 and 24) (Playgroup 201, Appendix 2, Table 6). The Day 0 culture of Participant 1026 was obtained prior to dosing and five days before any of the three vaccinees in this playgroup were vaccinated (November 23). Thus, it is not possible for this culture to be a vaccine virus. The Day 6 culture of Participant 1026 (November 24) was taken one day after the vaccination of vaccinees 1032,1036 and 1038 in this playgroup. It is highly unlikely that the vaccine viruses replicated in their upper airway, and were transmitted to Participant 1026 within a single day after dosing of the three vaccinees.

Participant 1001 shed type A virus on Day 15 (December 1) (Playgroup 101, Appendix 2, Table 7). No other participant in the playgroup of Participant 1001 shed type A virus; a single vaccinee (Participant 1005), shed vaccine virus type B five days earlier (November 26). Thus, the type A virus detected on Day 15 is unlikely to be vaccine virus unless non-detectable type A virus shed from one of the two vaccinees in this playgroup was transmitted to Participant 1001.

Overall, it appears not possible that Participant 1040 shed vaccine virus and unlikely that Participants 1026 and 1001 shed vaccine virus.

In summary, in this prospectively designed study there was a single confirmed transmission event. For this single event (Participant 1197), the probability of transmission is 0.0058 with an upper bound of the 95% confidence interval of 0.0170 (Table 38). The denominator used in this "all available" analysis is 93 placebo recipients instead of 99 because six of the children were in playgroups with no vaccine recipients and thus were not exposed to virus. Inclusion of a second event (Participant 1028) increased the probability to 0.0117 with an upper bound of the 95% CI of 0.0276 (Table 38). The highest probability of transmission if one includes the other two events (total of four events), which are unlikely to be true events, is 0.0236 with an upper bound of 0.0459.

Table 38
Estimated Transmission Rate in Study D145-P500

Population	n/N	Participants Included	Probability of Transmission (p)*	Upper Bound 95% CI
Confirmed case with all available analysis	1/93	1197	0.0058	0.0170
Confirmed + 1 possible case with all available analysis	2/93	1197, 1028	0.0117	0.0276
Confirmed + 2 possible case with all available analysis	3/93	1197, 1028, 1026	0.0176	0.0371
Confirmed + 3 possible case with all available analysis	4/93	1197, 1028, 1026, 1001	0.0236	0.0459

* Estimated using the Reed-Frost Model of transmission.

These transmission data are consistent with unpublished data presented at the November 1998 VRBPAC meeting by Dr. Peter Wright of Vanderbilt University School of Medicine who noted that vaccine virus may have been transmitted to two of 40 placebo children exposed to 108 vaccinees; 80 of the vaccinees were shown to shed vaccine virus.

11.3. Genetic Stability of CAIV and FluMist

The genetic stability of monovalent and bivalent formulations of CAIV has been examined in clinical studies conducted prior to the development of FluMist.

Twenty-one published studies, summarized in Table 39, have approached the issue of genetic stability by documenting that vaccine virus isolates recovered from susceptible adults or children retained the *ca, ts,* and/or *att* phenotype, and did not revert to a virulent phenotype.

Table 39
Summary of Historical Genetic Stability Studies

Reference	Vaccine Administered			Vaccine Recipients		No. with Phenotype / No. of Specimens Tested[a]		
	Type/Subtype		Strain	Serostatus	Age Group (N)	*ca*	*ts*	*att*
Murphy 1980	Monovalent	H1N1	A/Hong Kong/123/77	Seronegative	Adults (50)	62/62	62/62	NT[b]
Lazar 1980	Monovalent	H1N1	A/Hong Kong/123/77	Seronegative	Children (11)	NT	All[c]	NT
Wright 1982	Monovalent	H1N1	A/Hong Kong/123/77	Seronegative	Children (11)	NT	All	1/1
Belshe 1984	Monovalent	H1N1	A/California/10/78	Seronegative	Children (47)	NT	All	NT
Murphy 1984	Monovalent	H1N1	A/California/10/78	Seronegative	Adults (73)	29/29	29/29	NT
Steinhoff 1991	Monovalent	H1N1	A/Kawasaki/9/86	Seronegative	Children (39)	NT	10/10	NT
Gruber 1996	Monovalent	H1N1	A/Kawasaki/9/86	Seronegative	Children (44)	7/7	7/7	NT
Murphy 1981	Monovalent	H3N2	A/Alaska/6/77	Seronegative	Adults (24)	35/35	35/35	NT
Wright 1982	Monovalent	H3N2	A/Alaska/6/77	Seronegative	Children (10)	NT	9/9	NT
Clements 1983	Monovalent	H3N2	A/Alaska/6/77	Seronegative	Adults (66)	16/16	54/54	NT
Betts 1988	Monovalent	H3N2	A/Peking/2/79	Seronegative	Adults (72)	3/3	3/3	2/2
Clements 1984	Monovalent	H3N2	A/Washington/897/80	Seronegative	Adults (131)	29/29	38/38	NT
Gorse 1986	Monovalent	H3N2	A/Washington/897/80	Seropositive	Adults (27)	NT	2/2	NT
Anderson 1989	Monovalent	H3N2	A/Korea/1/82	Mixed	Children (24)	21/21	21/21	2/2
Steinhoff 1990	Monovalent	H3N2	A/Bethesda/1/85	Seronegative	Children (33)	NT	21/21	NT
Gruber 1996	Monovalent	H3N2	A/Los Angeles/2/87	Seronegative	Children (45)	16/16	16/16	NT
Keitel 1990	Monovalent	B	B/Texas/1/84	Seronegative	Adults (65)	All	All	NT
Anderson 1992	Monovalent	B	B/Texas/1/84	Mixed	Children (58)	13/13	13/13	NT
Clements 1990	Monovalent	B	B/Ann Arbor/1/86	Seronegative	Adults (32)	NT	3/3	NT
Edwards 1991	Monovalent	B	B/Ann Arbor/1/86	Seronegative	Children (43)	NT	195/195	NT
Miyazaki 1993	Monovalent	B	B/Ann Arbor/1/86	Mixed	High-risk Children (16)	1/1	1/1	NT
Davenport 1977	Bivalent	H3N2 B	A/Queensland/6/72 B/Hong Kong/8/73	Mixed	Adults (25)	NT	24/24	NT
Gruber 1996	Bivalent	H1N1 H3N2	A/Kawasaki/9/86 A/Los Angeles/2/87	Seronegative	Children (47)	26/26	26/26	NT
Miyazaki 1993	Bivalent	H1N1 H3N2	A/Kawasaki/9/86 A/Los Angeles/2/87	Mixed	High-risk Children (36)	3/3 1/1	3/3 1/1	NT NT
Miyazaki 1993	Trivalent	H1N1 H3N2 B	A/Kawasaki/9/86 A/Los Angeles/2/87 B/Ann Arbor/1/86	Mixed	High-Risk Children (19)	2/2 1/1 0/0	2/2 1/1 0/0	NT NT NT
Tanaka 1993	Trivalent	H1N1 H3N2 B	A/Kawasaki/9/86 A/Shanghai/11/87 B/Ann Arbor/1/86	Mixed	High-risk Children (68)	6/6 5/5 4/4	6/6 5/5 4/4	NT NT NT
TOTAL						280/280	591/591	5/5

[a] Includes either an isolate or an original nasopharyngeal specimen.

[b] "NT" indicates not tested.

[c] "All" indicates that all isolates maintained the vaccine phenotype, but the number of isolates tested was not reported.

The genetic stability of FluMist has been examined in four studies. In the first studies (Study AV002 and AV002-2), 68 H1N1, H3N2, and B isolates were characterized for *ts* phenotype and 28 isolates were characterized for genotype. All isolates tested maintained the 6:2 genotype and *ts* phenotype of the vaccine. In the third study (Study AV006), 18 culture-positive samples that were obtained during the two-week post-vaccination period were characterized for genotype and for the *ca* and *ts* phenotype. Each virus isolate tested retained the 6:2 genotype and the *ca* and *ts* phenotype of the vaccine strains.

The fourth study of the genetic stability FluMist consisted of genetic sequence and phenotypic analyses of virus isolates obtained from the clinical Study D145-P500 described above in Section 11.2, which was designed to directly assess transmissibility of FluMist among children 8 to 36 months of age in a daycare setting. Nasal swab specimens were obtained three times per week for three weeks. In order to maximize the likelihood of detecting changes in genetic sequence, samples originating from swabs taken at later times post-vaccination were chosen for sequence analyses, since nucleotide misincorporations would be expected to accrue with increased replication cycles. Genetic and phenotypic stability of FluMist during replication in vaccine recipients was assessed by comparison of the genomic sequence of the three viruses contained in the FluMist vaccine with the sequence of 56 independently derived virus isolates obtained from vaccinated children.

The results demonstrated that limited sequence alterations occur in vaccine viruses during replication in children, as would be expected for an RNA virus containing RNA polymerases that lack proofreading function. An average of 2 nucleotide differences per genome (ranging from zero to seven nucleotide misincorporations in the approximately 14 kilobase viral genome) was detected among the clinical virus isolates. Approximately 20% of the isolates were found to be identical to the vaccine strain administered, while approximately 50% of the isolates carried misincorporations detected in only one, or at most two, of the sequenced virus isolates. A restricted set of nucleotide changes (1–2 per vaccine virus strain) was detected in approximately 30% of the viruses sequenced. To determine whether any of the nucleotide substitutions found in the clinical virus isolates were also present in the original FluMist vaccine, clonal

analysis of selected regions of the vaccine strains was performed. The results demonstrated that of the six commonly detected nucleotide substitutions found in the clinical virus isolates, four were present as minor populations in the vaccine that were stable during replication in children. It is important to note that none of these nucleotide changes were at genetic loci previously reported to be associated with reversion of the ca and ts phenotype.

Regarding the single documented case of vaccine virus transmission in the daycare study in Finland, the genetic sequence of the Type B vaccine virus isolated from the placebo recipient (Subject 1197) was identical to that of the virus shed by the vaccine recipient (Subject 1204). Furthermore, the transmitted virus retained the *ca*, *ts*, and *att* phenotype and did not cause clinical signs and symptoms different from those of other study participants.

In conclusion, FluMist vaccine viruses were genetically stable and retained their cold-adapted, temperature-sensitive, and attenuated phenotype during replication in young children. The minor genetic changes detected were not at the genetic loci associated with attenuation, and did not disrupt the *ca*, *ts*, and *att* phenotype. In the single documented case of transmission, the transmitted virus was genetically and phenotypically stable, and did not appear to be associated with signs and symptoms that were different from those of other study participants.

11.4. Sensitivity of FluMist Vaccine Strains to Anti-Influenza Drugs

In considering the likely clinical outcome of transmission to individuals for whom FluMist is not recommended or is contraindicated, it should be kept in mind that FluMist vaccine strains are sensitive to anti-influenza drugs. MedImmune Vaccines has conducted laboratory studies of the drug sensitivity of six different H1N1, H3N2, and B FluMist vaccine strains and their wild-type parents to anti-influenza drugs (zanamivir, oseltamivir, amantidine, and rimantidine). The results demonstrated that each of the vaccine strains maintained the antiviral drug sensitivity of their wild-type parent (Tables 40 and 41).

Table 40
Susceptibility of Vaccine and Wild-Type Viruses to Zanamivir and Oseltamivir

Virus	IC_{50} (nM) of Zanamivir (Relenza®) [95% CI]	IC_{50} (nM) of Oseltamivir (Tamiflu®) [95% CI]
wt[a] A/Beijing/262/95	**0.065** [0.054-0.078]	**1.59** [1.08-2.37]
ca[b] A/Beijing/262/95	**0.086** [0.068-0.11]	**0.93** [0.37-2.32]
wt A/Sydney/05/97	**0.27** [0.15-0.49]	**0.25** [0.25-0.33]
ca A/Sydney/05/97	**0.32** [0.23-0.46]	**0.26** [0.20-0.33]
wt B/Beijing/243/97	**0.41** [0.28-0.62]	**7.06** [4.49-11.11]
ca B/Beijing/243/97	**0.43** [0.29-0.63]	**5.46** [3.76-7.94]
wt A/Wuhan/359/95	**0.25** [0.16-0.38]	**0.28** [0.22-0.36]
ca A/Wuhan/359/95	**0.34** [0.26-0.44]	**0.44** [0.33-0.59]
wt A/Shenzhen/227/95	**0.18** [0.14-0.24]	**1.78** [1.51-2.08]
ca A/Shenzhen/227/95	**0.21** [0.18-0.23]	**2.00** [1.74-2.30]
wt B/Yamanashi/166/98	**0.37** [0.26-0.50]	**8.07** [7.06-9.23]
ca B/Yamanashi/166/98	**0.50** [0.41-0.61]	**8.97** [7.41-10.86]
wt B/Ann Arbor/1/94	**0.46** [0.39-0.53]	**8.00** [6.76-9.46]
ca B/Harbin/7/94-like	**0.70** [0.43-1.16]	**7.44** [6.00-9.23]
wt A/Panama/2007/99	**0.28** [0.22-0.35]	**0.50** [0.45-0.57]
wt A/New Caledonia/20/99	**0.17** [0.15-0.19]	**1.16** [1.06-1.26]
wt B/Johannesburg/5/99	**0.26** [0.22-0.30]	**11.29** [9.12-13.96]
wt B/Victoria/504/2000	**2.46** [1.97-3.07]	**23.23** [20.69-26.08]
wt H1N1	**0.14** [0.11-0.18]	**1.29** [1.15-1.45]
wt H3N2	**1.42** [0.82-2.49]	**0.53** [0.39-0.75]
wt B	**0.43** [0.21-0.86]	**8.66** [5.93-12.7]
wt 274H	**0.10** [0.074-0.13]	**0.55** [0.38-0.79]
mutant 274Y[c]	**0.23** [0.097-0.53]	**343** [273-431]

[a] ″wt″ indicates wild-type viruses.
[b] ″ca″ indicates vaccine viruses.
[c] Tamiflu® resistant mutant.

The susceptibility of influenza virus to amantadine and rimantadine is conferred by the M2 gene of influenza A viruses. Influenza B strains do not encode a homologous proton channel and are not susceptible to this class of inhibitors. MedImmune Vaccines studies demonstrated that two vaccine strains containing the M segment from the influenza A master donor virus were sensitive to

amantadine and rimantadine, suggesting that all vaccine strains will be fully susceptible to these compounds (Table 41).

Table 41
Susceptibility of Vaccine Viruses to Amantadine and Rimantadine

Virus	IC_{50} (μM) of Amantadine	IC_{50} (μM) of Rimantadine
wt[a] A/Beijing/262/95	<5	<5
ca[b] A/Beijing/262/95	<5	<5
ca A/Sydney/05/97	<5	<5
ca B/Beijing/243/97	>160	>160
Mutant 294[c]	>20	>20

[a] ″wt″ indicates wild-type viruses.
[b] ″ca″ indicates vaccine viruses.
[c] Mutant 294 is rimantadine-resistant.

11.5. Summary

In summary, available data indicate that a low rate of transmission of FluMist may be expected among young children under conditions of close daily contact, but there is no evidence that transmission is accompanied by significant illness or loss of vaccine genotypic, phenotypic, and genetic characteristics. The overall risk associated with transmission of FluMist appears to be very low.

12. OVERALL CONCLUSIONS

FluMist is efficacious in preventing influenza in healthy children and healthy adults. Studies conducted in more than 20,000 children and adults have shown that FluMist is generally safe and well-tolerated in healthy children >60 months of age, healthy adolescents, and healthy adults through 64 years of age. Reactions associated with the vaccine primarily consist of mild upper respiratory tract signs and symptoms and have been self-limited. The high level of protective efficacy and the overall safety profile suggest a net benefit for FluMist in healthy children, adolescents, and adults 60 months to 64 years of age.