

5. SUMMARY OF EFFICACY

5.1. Introduction

Aviron has assessed the protective efficacy and/or effectiveness of FluMist in four completed clinical studies involving 4,653 healthy adults (Studies AV003 and AV009) and 1,602 healthy children (Studies AV006 and AV011). These studies are summarized in Table 2 by population, study number, design, number evaluated, key endpoints and results.

**Table 2
Summary of Completed FluMist Efficacy Studies**

Population	Study Number	Design	Number Evaluated	Key Endpoints	Results	
Healthy Adults	AV003	Randomized, double-blind, placebo controlled, challenge	92 ^a	Laboratory-documented illness	% Protection (CI)	
					85 (28, 100)	
	AV009	Randomized, double-blind, placebo controlled	4561	Proportion with any febrile illness (primary endpoint)	% Reduction (CI)	
					9.7 (-5.8, 22.8)	
					Days of:	
					Any febrile illness	22.9 (12.1, 32.4)
					Severe febrile illness	27.3 (16.7, 36.5)
					Febrile upper respiratory illness	24.8 (13.5, 34.7)
					Days of missed work due to:	
					Any febrile illness	13.1 (-0.9, 25.2)
Severe febrile illness	17.9 (4.3, 29.5)					
Febrile upper respiratory illness	28.4 (16.3, 38.8)					
Days of health-care provider visits due to:						
Any febrile illness	14.7 (-0.3, 27.5)					
Severe febrile illness	24.8 (11.6, 26.1)					
Febrile upper respiratory illness	40.9 (30.1, 50.0)					
Days of prescription antibiotic use due to:						
Any febrile illness	42.9 (33.1, 51.3)					
Severe febrile illness	47.0 (37.8, 54.9)					
Febrile upper respiratory illness	45.2 (35.2, 53.6)					
Healthy Children	AV006 Year One	Randomized, double-blind, placebo controlled	1602	Culture-confirmed illness	% Protection (CI)	
	AV006 Year Two		1358		93.4 (87.5, 96.5)	
	AV011	Randomized, double-blind, open label, challenge	222	Vaccine virus shedding	87.1 (77.7, 92.6)	
					82.9 (60.2, 92.7)	

^a 103 participants were enrolled in the study, 92 entered the challenge phase.

5.1.1. Clinical Efficacy Versus Clinical Effectiveness of Vaccination

The protective efficacy and effectiveness of an influenza vaccine can be assessed by any of several endpoints including 1) reduction in the signs and symptoms associated with clinical disease, 2) reduction in influenza infection as measured by the shedding of virus during infection and/or prevention of an increase in antibodies to viral proteins, or 3) reduction of influenza-related medical care or missed time from work or school.

Studies evaluating the protective efficacy of vaccine may rely either on community-based exposure to wild-type influenza or on direct experimental challenge with wild-type or vaccine virus.

Throughout this document, the term efficacy is used for measures of treatment benefit with culture confirmation. The term effectiveness is generally used for measures of treatment benefit regardless of the culture result. Study AV006 measured protection against community-acquired influenza in healthy children using the endpoint of culture-confirmed influenza virus associated illness during the influenza season directly following vaccination over two influenza seasons. In Study AV011, the endpoint for assessing protective efficacy of FluMist in children was the reduction in viral shedding of A/H1N1 vaccine virus following challenge in prior FluMist recipients compared to prior placebo recipients.

In Study AV003, the primary endpoint for assessing the protective efficacy of FluMist in healthy adults was laboratory-documented influenza illness following intranasal challenge with wild-type virus [i.e., symptoms consistent with influenza coupled with wild-type viral shedding and/or a fourfold or greater rise in the serum antibody titer of hemagglutination inhibition (HAI)]. Study AV009 measured protection against community-acquired, influenza-like illness in healthy working adults. In this study, the endpoints used to assess the effectiveness of FluMist were reductions in the occurrence of illness (proportion of participants with ≥ 1 episode), episodes of illness, days of illness and reduction in the illness-associated days of missed work, reduced work effectiveness, and healthcare utilization including health care provider visits, prescription antibiotic use, and over-the-counter medication use.

When evaluating the results of various outcome measures, it is important to distinguish between the efficacy and the effectiveness of a vaccine. Both can be evaluated in the context of a well designed controlled clinical trial and both measure reduction in outcomes; however, only those events that can be specifically related to influenza, such as laboratory-confirmed influenza, precisely address efficacy. In contrast, effectiveness is evaluated using less specific, but more

sensitive clinical outcomes usually in a real life context. Only some of these outcomes are directly related to influenza.

In Study AV006, both efficacy and effectiveness endpoints were assessed for certain outcomes. For example, in Year One of Study AV006, 97.5% efficacy against otitis media associated with culture-confirmed influenza was observed; however, there was a 35% reduction in febrile otitis media with antibiotic use in all vaccinees compared to placebo recipients regardless of the influenza culture result. This reduction is a measure of effectiveness, as it includes all events of febrile otitis media with antibiotic use during the study period. In the above example, confusing the clinical effectiveness with the efficacy would result in a substantial underestimation of the actual performance of a vaccine.

In Study AV009, which was also a randomized, double-blind, placebo-controlled study, only effectiveness measures were assessed. Cultures for influenza were taken in each of the 13 communities in the study to define the outbreak periods, but the individuals in the study cohort were not routinely cultured. The illness definitions in Study AV009 were selected to be highly sensitive and to reflect findings observed in daily clinical practice.

5.1.2. Statistical Methods

The beneficial effects of FluMist were measured in two clinical trials in adults, Study AV003 and Study AV009 and two clinical trials in children, Study AV006 (Year One and Year Two) and Study AV011. In adults, Study AV003 was a challenge trial for efficacy and Study AV009 was an effectiveness trial. In children, Study AV006 was a field trial of efficacy; Study AV011 was a challenge trial of efficacy. Therefore, owing to differences in participant populations and types of endpoints, only the single two-year trial (Study AV006) has been numerically combined with regard to efficacy.

In the single-year analyses for Study AV006, efficacy was computed using a simple proportion of participants who had culture-confirmed influenza. Koopman's method was used to calculate confidence intervals. The percent efficacy over two years and confidence intervals were estimated using Cox proportional hazards models.

The effectiveness endpoints in children were analyzed using the Wilcoxon Rank Sum test in the single-year analyses. Effectiveness in children (Study AV006) over two years and effectiveness in adults (Study AV009) was computed using Generalized Linear Models assuming an over dispersed Poisson model.

For outcomes involving proportions, efficacy and effectiveness were defined as $100\% \times [1 - (\text{proportion of FluMist recipients with at least one event} / \text{proportion of placebo recipients with at least one event})]$. For outcomes involving event rates (days of illness, number of episodes, etc.), efficacy and effectiveness were defined as $100\% \times [1 - (\text{event rate in FluMist group} / \text{event rate in placebo group})]$.

5.2. Healthy Adults

5.2.1. Efficacy of FluMist in Healthy Adults (Challenge Study AV003)

The Phase 3, randomized, double-blind, placebo-controlled trial, Study AV003, evaluated the efficacy of FluMist and a licensed trivalent injectable influenza vaccine (TIV) in relation to placebo for the prevention of laboratory-documented influenza illness in healthy adult participants who were challenged with wild-type influenza virus.

To be eligible for the assessment of vaccine efficacy, participants had to be serosusceptible at screening (HAI titer $\leq 1:8$) for at least one of the viruses contained in the vaccines (influenza types A/H1N1, A/H3N2, or B).

Study participants were stratified into three groups on the basis of strain serosusceptibility and then were assigned randomly (1:1:1) to one of three treatment groups (FluMist, TIV, or placebo). At time 0, each participant received an intranasal spray of 0.25 mL into each nostril (total dose of 0.5 mL) and an intramuscular injection of 0.5 mL as presented in Table 3.

**Table 3
Treatment Administered in Study AV003**

Treatment Group	Study Vaccines	
	Nasal Spray	Injection
FluMist	10^7 TCID ₅₀ types A/H1N1, A/H3N2, and B	0.01% Thimerosal in 0.01M PBS ^a
TIV	Allantoic fluid containing sucrose-phosphate-glutamate	Trivalent vaccine (TIV) ^b Fluvirin 1994/95
Placebo	Allantoic fluid containing sucrose-phosphate-glutamate	0.01% Thimerosal in 0.01M PBS ^a

^a PBS indicates phosphate buffered saline.

^b Fluvirin (1994/95 strains) manufactured by Evans Medeva, Liverpool, U.K.

The challenge phase of the study was initiated 28 days after vaccination, when participants were challenged with a virus strain to which they were susceptible at screening. Wild-type influenza challenge virus was delivered intranasally at a dose of 10^7 TCID₅₀ per 0.5 mL by drops

(0.25 mL into each nostril). Each of the three wild-type virus preparations contained one of the virus types represented in FluMist and TIV (influenza types A/H1N1, A/H3N2, or B). The participants were then sequestered and monitored twice daily for one week (Days 29–35) for fever and other clinical symptoms of influenza; nasal washes were taken daily for seven days after challenge to assess viral shedding. At Day 56, approximately 4 weeks after the wild-type viral challenge, participants returned for a final blood draw for HAI and brief physical exam.

5.2.1.1. Study AV003 Participant Disposition

The study enrolled healthy adults 18–41 years of age (mean, 25 years of age). One hundred three participants enrolled in the vaccination phase and 92 participated in the virus challenge phase (approximately 30 participants per treatment group). The cohort included 74% males and was racially diverse (52% White, 40% Black, 4% Hispanic, 4% Asian/Pacific Islander).

5.2.1.2. Efficacy of FluMist or TIV

The efficacy of FluMist or TIV was estimated relative to placebo using the following endpoints:

- a) viral shedding
- b) fourfold rise in HAI antibody titer
- c) any illness
- d) laboratory-documented influenza illness (c plus a or b above)

Laboratory-documented influenza illness for all three influenza strains combined was the endpoint of primary clinical significance. For the 92 participants challenged, the rates for this endpoint and each of the events contributing to it (viral shedding, fourfold rise in the post challenge HAI antibody titer and any illness) are presented in Table 4. The data are shown for each virus type and for all three types combined for each of the treatment groups.

Table 4
Vaccinees Responding to Challenge with Wild-Type Influenza Virus in Study AV003

Challenge Virus Type/Sub-type	Treatment Group	N	Viral Shedding n (%)	Fourfold Rise in HAI Antibody n (%)	Any Illness n (%)	Laboratory-documented Influenza Illness n (%)
A/H1N1	FluMist	10	3 (30)	2 (20)	5 (50)	1 (10)
	TIV	10	2 (20)	0 (0)	4 (40)	2 (20)
	Placebo	12	6 (50)	5 (50) ^a	7 (58)	6 (50)
A/H3N2	FluMist	9	3 (33)	2 (22)	2 (22)	1 (11)
	TIV	12	3 (25)	0 (0) ^b	7 (58)	2 (18) ^c
	Placebo	8	2 (25)	4 (50)	7 (88)	4 (50)
B	FluMist	10	1 (10)	2 (20)	4 (40)	0 (0)
	TIV	10	0 (0)	0 (0)	4 (40)	0 (0)
	Placebo	11	2 (18)	4 (36)	5 (45)	4 (36)
All	FluMist	29	7 (24)	6 (21)	11 (38)	2 (7)
	TIV	32	5 (16)	0 (0)	15 (47)	4 (13)
	Placebo	31	10 (32)	13 (45)	19 (61)	14 (45)

- ^a Excluded two placebo recipients with missing HAI data.
- ^b Excluded two TIV recipients with missing HAI data.
- ^c Excluded one TIV recipient missing HAI data and did not shed H3N2.

For all three virus types combined, 7% of the FluMist recipients, 13% of the TIV recipients, and 45% of the placebo recipients experienced laboratory-documented influenza illness (Table 4). Compared to placebo for all three viruses combined, the estimated efficacy of FluMist against laboratory-documented influenza illness was 85% (95% CI: 28, 100) and the estimated efficacy of TIV was 71% (95% CI: 2, 97) (Table 5). The confidence intervals for estimated efficacy are broad because of the small sample size. Strain-specific efficacy ranged from 78–100% for FluMist and from 60–100% for TIV. Thus, FluMist provided a highly significant degree of protection compared to placebo in preventing influenza infection accompanied by clinical symptoms.

Table 5
Percent Protective Efficacy of FluMist and TIV Relative to Placebo
for All Vaccinees after Challenge with Wild-Type
Influenza Virus by Virus Type in Study AV003

Challenge Virus Type/Sub-type	Treatment Group	Virus Shedding	Fourfold Rise in HAI Antibody	Any Illness	Laboratory-documented illness
A/H1N1	FluMist	40	60	14	80
	TIV	60	100	31	60
A/H3N2	FluMist	-33	56	75	78
	TIV	0	100	33	64
B	FluMist	45	45	12	100
	TIV	100	100	12	100
All	FluMist	25	54	38	85 (95% CI: 28, 100)
	TIV	52	100	24	71 (95% CI: 2, 97)

5.2.2. Effectiveness of FluMist in Healthy Adults (Study AV009)

Study AV009, a randomized, double-blind, placebo-controlled trial in healthy working adults 18–64 years of age, was designed to assess several measures of vaccine effectiveness. Specifically, the study was designed to test the ability of FluMist compared to placebo to reduce the occurrence of illness, number of illnesses, duration of illness and the illness-associated days of absenteeism from work and health care utilization in healthy adults during influenza outbreaks.

5.2.2.1. Illness Definitions

The primary effectiveness endpoint for the study was the proportion of participants reporting any febrile illnesses (AFI) during the peak outbreak periods. Participants were characterized as having any febrile illness 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. This characterization of illness was expected to be quite sensitive, but not necessarily specific, for true influenza illness. As such, a vaccine highly efficacious in preventing true influenza illness might be expected to have only moderate effect in reducing the occurrence of this event. Two additional pre-specified febrile illness syndromes which were expected to correlate with more severe illness and/or to have higher degree of specificity for true influenza illness were examined. These included severe febrile illness (SFI: at least three consecutive days of symptoms, at least one day of fever, two or more symptoms on at least three days) and febrile upper respiratory illness (FURI:

at least two consecutive days of upper respiratory symptoms [runny nose, sore throat, or cough], fever on at least one day, two symptoms on at least one day).

5.2.2.2. Study AV009 Participant Disposition

The study enrolled 4,561 adults 18–64 years of age (3,041 vaccinees and 1,520 placebo recipients). More than 97% of participants completed at least one effectiveness endpoint diary and 88% returned at least four of these five monthly diaries (Table 6). The proportions were similar between the two treatment groups.

**Table 6
Percent of Participants Returning Diary Cards by Month
and Treatment Group in Study AV009**

Treatment Group	November	December	January	February	March	At Least 1 of 5	At Least 4 of 5
FluMist	89.6%	91.1%	89.4%	89.3%	87.6%	97.0	87.7%
Placebo	90.4%	91.4%	89.5%	90.0%	87.8%	98.5	88.5%

5.2.2.3. Effectiveness Results

The proportion of participants experiencing one or more febrile illnesses (AFI) was lower among FluMist recipients, however, the 9.7% reduction was not statistically significant ($p = 0.19$) (Table 7).

**Table 7
Percentage of Participants with One or More Illness Events During
the Site-Specific Outbreak Periods in Study AV009**

Occurrence of:	FluMist N=2,833	Placebo N=1,420	Percent Reduction	p-value ^a
Any Febrile Illness ^b	13.2	14.6	9.7	0.19
Severe Febrile Illness	10.1	12.2	17.4	0.031
Febrile Upper Respiratory Illness	8.5	10.8	21.9	0.010

^a Unadjusted for multiple comparisons.

^b The primary endpoint of the study.

FluMist significantly reduced the proportion of participants with one or more severe febrile illnesses (SFI) (17.4% reduction, $p = 0.031$) and febrile upper respiratory illnesses (FURI) (21.9% reduction, $p = 0.010$). FluMist recipients had significantly fewer days of illness (p

≤0.0001) across the three pre-specified febrile illness definitions (Table 8); a 22.9% reduction for AFI, a 27.3% reduction for SFI, and a 24.8% reduction for FURI.

Table 8
Days of Illness during the Site-Specific Outbreak Periods in Study AV009

Days ^a of:	FluMist N=2,833	Placebo N=1,420	Percent Reduction	p-value ^b
Any Febrile Illness	1,188.0	1,541.2	22.9	0.0001
Severe Febrile Illness	1,021.1	1,404.5	27.3	<0.0001
Febrile Upper Respiratory Illness	875.7	1,164.7	24.8	<0.0001

^a Days per 1,000 participants per 7-week outbreak period.

^b Unadjusted for multiple comparisons.

In addition, those randomized to FluMist lost significantly fewer days of work (Table 9); a 17.9% reduction for SFI, and a 28.4% reduction for FURI. They also had significantly fewer days with health care provider visits, 24.8% reduction for SFI and a 40.9% reduction for FURI. Use of prescription antibiotics was significantly reduced by 42.9% to 47.0% and over the counter medications (OTC) were significantly reduced from 23.3% to 28.0% for the three pre-specified febrile illness definitions (Table 9). The illness-associated days of OTC medication, health care provider visits, prescription antibiotics and missed work were significantly reduced for upper respiratory illness (URI) regardless of fever (Table 9).

Table 9
Effects of FluMist during the Site-Specific Outbreak Periods in Study AV009

Illness-associated Days of:	Percent Reduction (95% CI)			
	Any Febrile Illness	Severe Febrile Illness	Febrile URI ^a	URI ^a
OTC Medication Use	23.3 ^b (12.0, 33.2)	27.6 ^c (16.5, 37.1)	28.0 ^c (16.8, 37.7)	11.3 ^d (1.0, 20.5)
Health-care Provider Visits	14.7 (-0.3, 27.5)	24.8 ^b (11.6, 36.1)	40.9 ^c (30.1, 50.0)	45.5 ^c (36.8, 53.0)
Prescription Antibiotics	42.9 ^c (33.1, 51.3)	47.0 ^c (37.8, 54.9)	45.2 ^c (35.2, 53.6)	29.1 ^c (18.0, 38.8)
Missed Work	13.1 (-0.9, 25.2)	17.9 ^d (4.3, 29.5)	28.4 ^c (16.3, 38.8)	19.4 ^e (7.5, 29.7)

^a URI indicates upper respiratory illness.
p-values unadjusted for multiple comparisons:

^b p<0.001,

^c p<0.0001,

^d p<0.05,

^e p<0.01.

5.2.2.4. Cross-Protection Against the A/Sydney Drifted Strain

The benefits of FluMist in reducing the illness and associated events were observed during a season in which the predominant circulating influenza virus strain, A/Sydney/05/97 (H3N2), was a drifted strain that was not included in the vaccine. While the effectiveness of FluMist might have been even greater with a match between the circulating virus and vaccine strains, FluMist appears to have given the adults in this study substantial protection against the drifted strain, A/Sydney/05/97 (H3N2). Cross-protection against culture-confirmed disease due to this drifted strain during the same season was also demonstrated in children who received FluMist in Year Two of the Pediatric Protective Efficacy Trial, Study AV006; 85.9% efficacy (95% CI: 75.3, 91.9).

5.2.3. Conclusions

The data from two Phase 3 studies in healthy adults (Study AV003 and Study AV009) show that FluMist was both efficacious and effective. They compliment data from prior NIH studies showing that CAIV was highly effective and comparable to TIV in preventing illness.

The data from Study AV003 in healthy adults showed that FluMist compared to placebo (vaccine efficacy = 85%) was as protective as TIV compared to placebo (vaccine efficacy = 71%) in preventing laboratory-documented influenza illness among healthy adult vaccinees challenged with wild-type influenza A/H1N1 or A/H3N2 or B viruses. The data from the effectiveness trial in healthy adults, Study AV009, showed that FluMist recipients experienced statistically significant reductions in the number of days of febrile illness regardless of the definition (any febrile illness, severe febrile illness, or febrile upper respiratory illness) by 22.9% to 27.3%. Furthermore, the proportion of participants with severe febrile illness (SFI) and febrile upper respiratory illness (FURI) were significantly reduced by 17.4% ($p = 0.031$) and 21.9% ($p = 0.010$), respectively. In addition to the clinical effect, FluMist recipients experienced fewer days of missed work, fewer health care provider visits, less prescription antibiotic use, and less over-the-counter medication use. The efficacy and effectiveness data from Studies AV003 and AV009 add to the extensive data in the literature on the efficacy of CAIV. FluMist can be expected to substantially reduce the clinical and economic impact of influenza illness in healthy adults.

5.3. Healthy Children

Children experience significant morbidity from influenza and are important transmitters of influenza virus. The highest attack rates in children are at least 3-fold higher than those observed in adults.

5.3.1. Efficacy in Healthy Children (Study AV006)

Study AV006, a Phase 3, randomized, double-blind, placebo-controlled trial conducted at 10 geographically distributed study centers in the United States, evaluated the efficacy of FluMist in preventing community-acquired, culture-confirmed influenza illness in healthy children 15 to 71 months of age at first vaccination. The trial was designed as a two-year study with a single cohort recruited in Year One, to be re-vaccinated without re-randomization (i.e., remain in their original treatment group assignment, vaccine or placebo) in Year Two. In Year One the study assessed protection among children who received a one or two-dose primary FluMist series compared to placebo. In Year Two the study assessed protection of a single dose of FluMist among children who previously received a one or two-dose regimen in Year One.

5.3.1.1. Study AV006 Year One Participant Disposition

A total of 1,602 children 15 to 71 months of age (had not reached their sixth birthday) were enrolled in the study. They were randomized 2:1 to receive either FluMist or placebo delivered as 0.5 mL by nasal spray (0.25 mL into each nostril). Children received either one or two doses, but enrollment into the dosing regimen was not randomized.

The study was designed primarily to assess the two-dose regimen; 1,314 of the 1,602 study participants (82%) were enrolled to receive two doses of vaccine or placebo. However, because in any given influenza season a child might only receive a single dose before an influenza outbreak, it was useful to include a one-dose cohort. Two hundred eighty-eight of the children (18%; primarily at two of the ten study sites) received only a single dose of vaccine or placebo. For children who received two doses, the second dose was scheduled 60 ± 14 days after the first dose. There was a high level of compliance; 97% of the 1,314 children enrolled to receive two doses of vaccine or placebo actually received their second dose. The number of participants in Year One in each treatment group by dosing regimen are presented in Table 10.

Table 10
Number of Participants in Each Treatment Group
by Dosing Regimen in Study AV006 Year One

Regimen	FluMist	Placebo	Total
One Dose	189	99	288
Two Doses	881	433	1314
Total	1070	532	1602

5.3.1.2. Efficacy of FluMist in Study AV006 Year One

Culture-Confirmed Influenza Illness

Children were monitored via regular telephone contacts with parents/guardians for signs and symptoms of possible influenza, and when established criteria were met, viral cultures for influenza were obtained.

Overall, 14 (1.3%) of the 1070 FluMist recipients experienced culture-confirmed influenza illness compared to 94 (17.7%) of the 532 placebo recipients (Table 11). No FluMist recipient had both influenza A and B infections; however, six children in the placebo group had Type A/H3N2 influenza followed by Type B influenza. Therefore, 94 placebo recipients had 100 cases of culture-confirmed influenza illness. Of the 114 influenza cases in 108 children, 70 (61%) were caused by Type A/Wuhan (H3N2) virus, and 44 (39%) were caused by Type B/Harbin. Both wild-type strains circulating during the 1996–1997 influenza season were antigenically matched to the vaccine strains.

Table 11
Cases of Culture-Confirmed Influenza in
Study AV006 Year One

Strain	FluMist N=1070	Placebo N=532
	Number (%) of Cases	Number (%) of Cases
Any	14 (1.3)	94 (17.7) ^a
H3N2	7 (0.7)	63 (11.8)
B	7 (0.7)	37 (7.0)

^a Sum of H3N2 and B cases exceeds the total for "any" because 6 children in the placebo group had both H3N2 and B influenza.

The vaccine was highly efficacious, with an estimated overall efficacy of 93.4% (95% CI: 87.5, 96.5) for the primary endpoint of protection against culture-confirmed influenza illness in children who received two doses. The estimated efficacy was 92.6% (95% CI: 87.3, 95.7) for all children enrolled to receive either one or two doses (Table 12). Among all randomized children, the estimated strain-specific efficacy was 94.5% (95% CI: 88.3, 97.4) for protection against A/H3N2 and 90.6% (95% CI: 79.5, 95.7) for protection against influenza B.

Table 12
Efficacy of FluMist in Preventing Culture-Confirmed
Influenza Illness in Study AV006 Year One

Analysis Group	Strain	Number of Isolates			Estimated Efficacy %	95% Confidence Interval %
		FluMist	Placebo	Total		
Two Doses Received ^a	Any	10	73	83	93.4	(87.5, 96.5)
	H3N2 ^b	4	48	52	96.0	(89.4, 98.5)
	B ^c	6	31	37	90.5	(78.0, 95.9)
All Participants	Any	14	94	108	92.6	(87.3, 95.7)
	H3N2	7	63	70	94.5	(88.3, 97.4)
	B	7	37	44	90.6	(79.5, 95.7)
Enrolled in Two-Dose Regimen	Any	11	80	91	93.2	(87.6, 96.3)
	H3N2	5	55	60	95.5	(89.3, 98.1)
	B	6	31	37	90.5	(78.0, 95.9)
Enrolled in One-Dose Regimen	Any	3	14	17	88.8	(64.5, 96.5)
	H3N2	2	8	10	86.9	(46.6, 96.8)
	B	1	6	7	91.3	(45.6, 98.6)

- ^a Primary Endpoint was efficacy in children who received two doses.
- ^b Excludes eight participants who had H3N2 disease prior to receiving the second dose and five participants who received FluMist or TIV before entry into the trial.
- ^c Excludes five participants who received FluMist or TIV prior to entry into the trial.

A single dose of FluMist protected nearly as well as a two-dose regimen for the two wild-type influenza viruses (Type A/H3N2 and Type B) that circulated in the 1996–1997 influenza season; estimated overall efficacy was 88.8% (95% CI: 64.5, 96.5). The estimated efficacy was 86.9% (95% CI: 46.6, 96.8) for protection against culture-confirmed influenza Type A/H3N2 and 91.3% (95% CI: 45.6, 98.6) for influenza B. Given the smaller number of children receiving the single dose regimen in the study, the confidence intervals are wider. The study results support the conclusion that one or two doses of FluMist provides protection for Type A/H3N2 and for Type B strains.

In Year One, there were four cases of influenza-associated lower respiratory illness (LRI) defined as healthcare provider documented croup, bronchiolitis, pneumonia, or wheezing illness. The estimated efficacy was 83.4% (95% CI: -15.4, 97.6) with three of the four cases of LRI occurring in the placebo group. Influenza-associated LRI data for Year One, Year Two, and both years combined is presented in Table 22.

Febrile Illness and Otitis Media

In addition to the primary endpoint of culture-confirmed influenza, Study AV006 demonstrated that vaccination with FluMist substantially reduced the incidence of febrile illness associated with influenza and otitis media associated with influenza. The estimated efficacy relative to placebo was 95.0% (95% CI: 90.0, 97.5) for protection against febrile illness and the estimated efficacy was 97.5% (95% CI: 85.5, 99.6) for protection against otitis media (Table 13).

Table 13
Efficacy of FluMist in Preventing Culture-Confirmed Influenza Accompanied by Fever or Otitis Media for All Randomized Participants in Study AV006 Year One

Endpoint	FluMist N=1070 n (%)	Placebo N=532 n (%)	%Efficacy (95% CI)
Febrile ^a Illness	8 (0.7)	80 (15.0)	95.0 (90.0, 97.5)
Otitis Media	1 (0.1)	20 (3.8)	97.5 (85.5, 99.6)

^a Febrile defined as temperature $\geq 101^{\circ}\text{F}$, rectal, or $\geq 101^{\circ}\text{F}$, oral, or $\geq 100.4^{\circ}\text{F}$, axillary.

Vaccination with FluMist also significantly reduced, by one third, the overall occurrence of febrile illness and febrile otitis media, and the associated antibiotic use for these conditions among all vaccinees compared to placebo recipients, regardless of influenza culture result (Table 14).

Other Pre-specified Outcome Measures in Year One

Statistically significant reductions were observed for days of missed daycare/preschool/school, parent lost work and health care provider visits associated with culture-confirmed influenza illness ($p < 0.01$). In addition, FluMist significantly reduced the overall number of health care provider visits over the influenza season among vaccinated children compared to placebo recipients regardless of the influenza culture result ($p = 0.02$). Reductions were also observed for days of missed daycare/preschool/school and parental lost work among all vaccinees compared

to placebo recipients, regardless of the influenza culture result, but these reductions were not statistically significant (Table 14).

Table 14
Efficacy and Effectiveness of FluMist in Study AV006 Year One

Endpoint	FluMist ^a	Placebo ^a	Percent Reduction	p-value ^b
Febrile illness with antibiotics ^{c, d}	0.31	0.46	31.0	<0.01
Febrile otitis media with antibiotics ^{c, d}	0.14	0.22	35.0	<0.01
Missed daycare/preschool/school days				
All illness ^c	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 ^c	0.26	0.31	16.8	0.24
Culture-positive illness	0.00 ^e	0.08	97.7	<0.01
Healthcare provider visits				
All illness ^c	1.20	1.39	13.4	0.02
Culture-positive illness	0.01	0.14	93.9	<0.01

^a Rate per participant.

^b Unadjusted for multiple comparisons, Wilcoxon Rank Sum test.

^c For all participants with illness events regardless of the influenza culture result.

^d Febrile defined as temperature $\geq 101^{\circ}\text{F}$, rectal, or $\geq 101^{\circ}\text{F}$, oral, or $\geq 100.4^{\circ}\text{F}$, axillary.

^e Exact value is 0.0019.

5.3.1.3. Study AV006 Year Two Participant Disposition

A total of 1,358 (85%) of the 1,602 children enrolled in the Year One study re-enrolled in Year Two of Study AV006. These children remained in their original treatment group and received a single dose of vaccine or placebo regardless of the dosing regimen in Year One (Table 15).

Table 15
Number of Participants in Study AV006 Year Two by Treatment Group and Year One Dosing Regimen

Regimen in Year One	FluMist	Placebo	Total
One Dose	162	77	239
Two Doses	755	364	1119
Total	917	441	1358

5.3.1.4. Efficacy of FluMist in Study AV006 Year Two

Culture-Confirmed Influenza Illness

As in Year One, children were monitored for signs and symptoms of possible influenza, and, when established criteria were met, viral cultures for influenza were obtained.

There were 71 cases of culture-confirmed influenza illness. Sixty-six were caused by a newly emergent strain A/Sydney (H3N2), and five were caused by strains similar to the vaccine strains [four A/Wuhan (H3N2) and one influenza B]. Among FluMist recipients, 15 of 917 (2%) experienced culture-confirmed influenza illness compared to 56 of 441 (13%) placebo recipients (Table 16).

**Table 16
Cases of Culture-Confirmed Influenza
in Study AV006 Year Two Participants**

FluMist N = 917 n (%)	Placebo N = 441 n (%)
15 (2)	56 (13)

The vaccine was highly efficacious overall with an estimated efficacy of 87.1% (95% CI: 77.7, 92.6) against culture-confirmed influenza illness (Table 17). The vaccine efficacy was 100% (95% CI: 63.1, 100) against the circulating strains represented in the vaccine [four A/Wuhan (H3N2) isolates and one influenza B isolate].

The estimated strain-specific efficacy was 86.9% (95% CI: 77.2, 92.5) against Type A/H3N2 and 100% against Type B (Table 17). The vaccine provided excellent heterotypic immunity against the variant strain A/Sydney (H3N2) with an estimated efficacy of 85.9% (95% CI: 75.3, 91.9).

Table 17
Efficacy of FluMist in Preventing Culture-Confirmed Influenza Illness in All Year Two Participants in Study AV006

Strain	Number of Isolates			Estimated Efficacy %	95% Confidence Interval
	FluMist	Placebo	Total		
All Community-Acquired Strains (A/Wuhan, A/Sydney, B ^a)	15	56	71	87.1	(77.7, 92.6)
Strains in FluMist (A/Wuhan, B ^a)	0	5	5	100	(63.1, 100)
All A/H3N2	15	55	70	86.9	(77.2, 92.5)
A/Wuhan	0	4	4	100	(53.9, 100)
A/Sydney	15	51	66	85.9	(75.3, 91.9)

^a There was only one case of influenza B which occurred in a placebo recipient.

Four of the 70 Type A/H3N2 cases in Year Two occurred in placebo recipients in the one-dose regimen in Year One; the efficacy in this subgroup was 100% (95% CI: 54.9, 100). The efficacy for A/H3N2 in Year Two for those in the two-dose regimen in Year One was 85.8% (95% CI: 75.3, 91.9). Therefore, a single re-vaccinating dose of FluMist in Year Two protected those children who received one or two doses in Year One of the trial. The estimated efficacy for Type A/H3N2 in Year Two of 86.9% is lower than that of Year One, 94.3% for Type A/H3N2 (Table 12), which is likely due to the predominance of the drifted strain A/Sydney (H3N2) in Year Two.

In Year Two, there were eight cases of influenza-associated lower respiratory illness (LRI) defined as healthcare provider documented croup, bronchiolitis, pneumonia, or wheezing illness. The estimated efficacy was 100% (95% CI: 77.0, 100) with all eight cases of LRI occurring in the placebo group. In addition, all LRI cases were due to A/Sydney (H3N2). These data for Year One, Year Two and both years combined are presented in Table 22.

Protection from Illness by Wild-Type Disease

Natural infection of children with wild-Type A/H3N2 influenza in Year One protected against influenza illness in Year Two. Of 52 placebo recipients who were culture-positive for A/H3N2 in Year One, only 1 (1.9%) was positive for A/H3N2 influenza illness in Year Two (Table 18). In contrast, of 389 placebo recipients without culture-positive influenza A/H3N2 in Year One, 54 (13.9%) had culture-confirmed A/H3N2 illness in Year Two. The estimated efficacy of natural A/H3N2 infection in Year One against wild-type A/H3N2 infection in Year Two was 86.1% (95%

CI: 25.9, 97.6) which is similar to the protection of 86.9% (95% CI: 77.2, 92.5) afforded by FluMist (Table 17). Thus, vaccination with FluMist provided a level of protection similar to that of prior natural infection, but without influenza-associated disease.

Table 18
Protection of Natural Infection in Study AV006 Year One against A/H3N2
Influenza Illness in Study AV006 Year Two for the Placebo Group

Wild-Type A/H3N2 Influenza Illness in Year One	Wild-Type A/H3N2 Influenza Illness in Year Two			Efficacy = 86.1% (95% CI: 25.9, 97.6)
	No n (%)	Yes n (%)	Total n	
Yes	51 (98)	1 (1.9)	52	
No	335 (86)	54 (13.9)	389	

Febrile Illness and Otitis Media

In Year Two, FluMist significantly reduced the incidence of febrile illness and otitis media associated with influenza. The estimated efficacy relative to placebo was 89.3% (95% CI: 80.4, 94.2) against culture-confirmed influenza-associated febrile illness and 94.3% (95% CI: 78.1, 98.5) against culture-confirmed influenza-associated otitis media (Table 19). In Year Two, FluMist also reduced the overall occurrence of febrile otitis media with associated antibiotic use among all vaccinees regardless of the influenza culture result (Table 20).

Table 19
Efficacy of FluMist in Preventing Culture-Confirmed Influenza
Accompanied by Fever or Otitis Media for All Randomized
Participants in Study AV006 Year Two

Endpoint	FluMist N = 917 n (%)	Placebo N = 441 n (%)	% Efficacy (95% CI)
Febrile Illness	12 (1.3)	54 (12)	89.3 (80.4, 94.2)
Otitis Media	2 (0.2)	17 (4)	94.3 (78.1, 98.5)

Note: Febrile defined as temperature $\geq 101^{\circ}\text{F}$, rectal, or $\geq 101^{\circ}\text{F}$, oral, or $\geq 100.4^{\circ}\text{F}$, axillary.

Other Pre-specified Outcome Measures in Year Two

In Year Two of the trial, statistically significant reductions were observed for days of missed daycare/preschool/school, parent lost work, and healthcare provider visits associated with culture-confirmed influenza illness ($p < 0.01$) (Table 20). In addition, FluMist significantly reduced the overall number of days of missed daycare/preschool/school over the influenza season among vaccinated children compared to placebo recipients, regardless of the influenza culture result ($p = 0.01$). Reductions were also observed for days of parental lost work and healthcare provider visits among all vaccinees compared to placebo recipients, regardless of the influenza culture result, but these reductions were not statistically significant.

Table 20
Efficacy and Effectiveness of FluMist in Study AV006 Year Two

Endpoint	FluMist ^a	Placebo ^a	Percent Reduction	p-value ^b
Febrile illness with antibiotics ^{c, d}	0.30	0.34	10.6	0.18
Febrile otitis media with antibiotics ^{c, d}	0.11	0.13	20.9	0.04
Missed daycare/preschool/school				
All illness ^c	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 ^c	0.29	0.32	8.7	0.37
Culture-positive illness	0.01	0.07	87.8	<0.01
Healthcare provider visits				
All illness ^c	0.95	1.02	7.0	0.18
Culture-positive illness	0.01	0.09	88.9	<0.01

^a Rate per participant.

^b Unadjusted for multiple comparisons, Wilcoxon Rank Sum test.

^c For all participants with illness events regardless of the influenza culture result.

^d Febrile defined as $\geq 101^\circ\text{F}$, rectal, or $\geq 101^\circ\text{F}$, oral, or $\geq 100.4^\circ\text{F}$, axillary.

5.3.1.5. Efficacy and Effectiveness Results in Study AV006 Year One and Year Two Combined

In Year One, 1,070 children were vaccinated with FluMist and 532 children received placebo (2:1 randomization). In Year Two, 917 of the 1,070 FluMist recipients (86%) returned and were re-vaccinated. In the placebo group, 441 of the 532 original children (83%) returned for dosing in Year Two. For both study years combined, 29 FluMist recipients experienced culture-confirmed influenza illness compared to 147 placebo recipients (Table 21). A total of 185 influenza cases were reported in 176 children; nine children had more than one culture-

confirmed illness and all were in the placebo group. In Year One, six children had Type A illness followed by Type B. Three other children had disease in both years, two children with type B illness in Year One had type A influenza in Year Two, and one child with Type A/Wuhan (H3N2) in Year One had Type A/Sydney (H3N2) influenza in Year Two.

FluMist was highly efficacious with an estimated overall efficacy of 91.7% (95% CI: 87.7, 94.4) against culture-confirmed influenza illness (Table 21). The estimated strain-specific efficacy was 91.9% (95% CI: 87.2, 94.9) for Type A (H3N2) strains and 91.1% (95% CI: 80.1, 96.0) for Type B. Thus, combined data from both trial years showed that FluMist protected children against influenza.

**Table 21
Overall Efficacy of FluMist in Preventing Culture-Confirmed Influenza Illness
in Study AV006 Year One and Year Two Combined for All Participants**

Strain	Number of Children with ≥ 1 Positive Culture		Estimated Efficacy %	95% Confidence Interval %
	FluMist ^a	Placebo ^b		
All community-acquired strains (A/Wuhan, A/Sydney, B)	29	147	91.7	(87.7, 94.4)
All A/H3N2 (A/Wuhan, A/Sydney)	22	117	91.9	(87.2, 94.9)
All B	7	38	91.1	(80.1, 96.0)

^a 1070 vaccinees in Year One with 917 returning in Year Two.

^b 532 placebo recipients in Year One with 441 returning in Year Two.

Lower Respiratory Illness Associated with Positive Influenza Cultures

FluMist was highly efficacious at preventing lower respiratory disease associated with influenza; the combined efficacy for both years was 95.2% (95% CI: 62.2, 99.4) (Table 22).

Table 22
Efficacy of FluMist in Preventing Lower Respiratory Illness Associated with Culture-Confirmed Influenza in Study AV006 Year One, Year Two and Both Years Combined

Group Analyzed	Number of Illnesses		Estimated Efficacy %	95% CI	p-value
	FluMist ^a	Placebo ^b			
AV006 Year One	1	3	83.4	(-15.4, 97.6)	0.08
AV006 Year Two	0	8	100	(77.0, 100)	<0.001
Year One and Year Two Combined	1	11 ^c	95.2	(62.2, 99.4)	0.004

^a 1070 vaccinees in Year One with 917 returning in Year Two.

^b 532 placebo recipients in Year One with 441 returning in Year Two.

^c One person had an illness in both years. The analysis considers only the first event.

Other Outcome Measures for Years One and Two Combined

For both study years combined, FluMist significantly reduced the incidence of influenza-associated febrile illness [vaccine efficacy of 93.6% (95% CI: 89.7, 96.0)] and of influenza-associated otitis media [vaccine efficacy of 96.2% (95% CI: 87.6, 98.8)] (Table 23).

Table 23
Efficacy of FluMist for All Randomized Participants in Preventing Culture-Confirmed Influenza Accompanied by Fever or Otitis Media in Study AV006 Year One and Year Two Combined for All Participants

Endpoint	FluMist ^a n (%)	Placebo ^b n (%)	% Efficacy (95% CI) ^c
Febrile Illness	20 (1.9)	134 (25.0) ^d	93.6 (89.7, 96.0)
Otitis Media	3 (0.3)	37 (7.0)	96.2 (87.6, 98.8)

Note: Febrile defined as temperature $\geq 101^{\circ}\text{F}$, rectal, or $\geq 101^{\circ}\text{F}$, oral, or $\geq 100.4^{\circ}\text{F}$, axillary.

^a 1070 vaccinees in Year One with 917 returning in Year Two.

^b 532 placebo recipients in Year One with 441 returning in Year Two.

^c Efficacy and confidence intervals were estimated using Cox Proportional Hazards models.

^d One person had an illness in both years. The analysis considered only the first event.

FluMist also significantly reduced three additional influenza-associated endpoints by $\geq 92.1\%$ ($p < 0.0001$) for both study years combined: days of missed daycare/preschool/school; parental lost work days; and the number of health care provider visits (Table 24).

For both study years combined, regardless of the influenza culture result, FluMist significantly reduced febrile illness with antibiotic use by 23.3% ($p = 0.0002$) and febrile otitis media with antibiotic use by 30.4% ($p < 0.0001$) (Table 24).

Consistent reductions were observed for the other outcome measures for the FluMist group compared to the placebo group regardless of the influenza culture result. The number of health care provider visits was reduced for both years combined by 11.2% ($p = 0.02$) (Table 24). The number of days of missed daycare/preschool/ school were reduced by 12.8% ($p = 0.07$). Parental lost work days were reduced by 12.6% ($p = 0.17$) (Table 24). However, this latter reduction may be an underestimate as lost work days for a parent who worked at home were not collected.

Table 24
Effectiveness and Efficacy of FluMist in Study AV006 Year One and Year Two Combined

Endpoint	FluMist ^a	Placebo ^a	Percent Reduction	p-value ^b
Febrile illness with antibiotics ^{c, d}	0.309	0.403	23.3	0.0002
Febrile otitis media with antibiotics ^{c, d}	0.126	0.181	30.4	<0.0001
Missed daycare/preschool/school				
All illness ^c	0.824	0.946	12.8	0.07
Culture positive illness	0.013	0.193	93.2	<0.0001
Parental lost work days				
All illness ^c	0.263	0.301	12.6	0.17
Culture positive illness	0.005	0.072	93.0	<0.0001
Healthcare provider visits				
All illness ^c	1.087	1.223	11.2	0.02
Culture positive illness	0.009	0.115	92.1	<0.0001

^a Rate per participant, computed using Generalized Linear Models assuming an over dispersed Poisson Model.

^b Unadjusted for multiple comparisons.

^c For all participants with illness events regardless of the influenza culture result.

^d Febrile defined as temperature $\geq 101^\circ\text{F}$, rectal or $\geq 101^\circ\text{F}$, oral, or $\geq 100.4^\circ\text{F}$, axillary.

5.3.2. Efficacy of FluMist Against H1N1 (Vaccine Challenge Study AV011)

Since A/H1N1 virus did not circulate in the United States during either year of AV006. Study AV011 was initiated following the conclusion of the Year Two influenza season in the spring of 1998. A surrogate measure to estimate the protective efficacy of FluMist against this virus subtype was used. The primary objective in Study AV011 was to assess the efficacy of FluMist against viral shedding after challenge with a monovalent A/H1N1 vaccine virus (CAIV-M).

It was expected that persons effectively immunized against A/H1N1 by prior vaccination with FluMist would be less likely than prior placebo participants to develop an infection resulting in shedding of virus when challenged with CAIV-M.

Children who completed both years of Study AV006 were considered eligible for Study AV011: Two hundred twenty-two children (144 prior FluMist recipients and 78 prior placebo recipients) were challenged intranasally with monovalent Type A Shenzhen/227/95 (H1N1) vaccine five to eight months (mean of 223 days) after their second annual vaccination with FluMist. To assess viral shedding, nasal and throat swabs were taken daily for four consecutive days beginning the day after challenge with CAIV-M.

After challenge, 4% (6 of 142) of prior FluMist recipients and 25% (19 of 77) of prior placebo recipients shed CAIV-M. Thus, the efficacy of FluMist against shedding of the H1N1 challenge strain was 82.9% (95% CI: 60.2, 92.7) (Table 25). The number of days of shedding CAIV-M was significantly reduced in the prior FluMist recipients compared to the prior placebo recipients ($p = 0.0001$).

Table 25
H1N1 Shedding in Study AV011 by
Treatment Group in Study AV006

Shedding	All	
	Prior FluMist N = 142	Prior Placebo N = 77
Shedding on Any Day ^a		
Yes	6 (4%)	19 (25%)
No	136 (96%)	58 (75%)
Days of Shedding ^b		
0	136 (96%)	58 (76%)
1	4	12
2	2	4
3	0	2
4	0	0
Mean	0.06	0.34

Efficacy = 82.9%
 (95% CI: 60.2, 92.7)

Note: One prior placebo recipient of 78 enrolled and two prior FluMist recipients of 144 enrolled are excluded from Shedding on Any Day analysis because of missing shedding results. One additional prior placebo recipient is excluded from Days of Shedding analysis because of missing shedding results (N = 76).

^a Test of ratio of two binomial proportions using Koopman's approach, $p < 0.0001$.

^b Wilcoxon Rank Sum test, $p = 0.0001$.

Serum HAI antibodies and nasal wash IgA antibodies were measured prior to the CAIV-M vaccine virus challenge. Table 26 presents shedding by prior treatment group and pre-challenge HAI serostatus. Ninety-six of 141 (68%) participants who previously received FluMist had serum HAI antibody titers $\geq 1:8$ at the time of challenge (5 to 8 months post vaccination) as compared to 25 of 75 (33%) participants who had previously received placebo. Not surprisingly, there was a strong correlation in the placebo group between presence of HAI antibodies prior to challenge and the lack of virus shedding after challenge ($p = 0.0001$). Notably, when the seronegative children (those with HAI titers $\leq 1:4$) are considered, only 4 of 45 (9%) prior vaccinees shed CAIV-M compared to 19 of 50 (38%) children who shed in the former placebo group ($p = 0.0015$).

Table 26
Shedding of H1N1 Vaccine Virus by Group and Pre-Challenge Serum HAI Antibody Status in Study AV011

Prior FluMist		Prior Placebo	
HAI Negative ≤1:4 ^a n/N	HAI Positive ≥1:8 n/N	HAI Negative ≤1:4 ^{a, b} n/N	HAI Positive ≥1:8 ^b n/N
4/45 (9%)	2/96 (2%)	19/50 (38%)	0/25 (0%)

^a Shedding in HAI negative prior vaccinees versus shedding in HAI negative prior placebo recipients; 4 of 45 versus 19 of 50; p=0.0015 by Fisher's Exact test.

^b p = 0.0001 by Fisher's Exact test for placebo group.

Likewise, the presence of pre-challenge nasal IgA antibody was associated with protection from vaccine virus challenge. Among the previously vaccinated children with pre-challenge nasal IgA, only 1 of 88 (1%) shed vaccine virus (Table 27). Among participants who lacked detectable nasal IgA, 5 of 41 (12%) previously vaccinated recipients and 16 of 44 (36%) prior placebo recipients shed challenge virus (p =0.012). Significantly more previously vaccinated children with no HAI and no nasal IgA detected had serum microneutralizing antibody than did prior placebo recipients (12 of 16 versus 1 of 35, respectively; p<0.001). These data suggest that while serum HAI, serum microneutralizing, and nasal IgA antibodies may contribute to protection, FluMist apparently prevents shedding of challenge virus by additional mechanisms.

Table 27
Shedding of H1N1 Vaccine Virus by Group and Pre-Challenge Nasal IgA Antibody Status in Study AV011

Prior FluMist		Prior Placebo	
IgA Negative ^a n/N	IgA Positive n/N	IgA Negative ^{a, b} n/N	IgA Positive ^b n/N
5/41 (12%)	1/88 (1%)	16/44 (36%)	3/23 (13%)

^a Shedding in IgA negative prior vaccinees versus shedding in IgA negative prior placebo recipients; 5 of 41 versus 16 of 44; p=0.012 by Fisher's Exact test.

^b p = 0.051 by Fisher's Exact test for placebo group.

In summary, FluMist was 82.9% efficacious in preventing shedding after intranasal challenge with 10⁷ TCID₅₀ cold-adapted, live attenuated monovalent influenza vaccine A/Shenzhen/227/95 (H1N1). Immunity is associated with antibodies in serum and IgA antibodies in nasal wash fluid;

however, the vaccine appears to protect by additional mechanisms. These data and the efficacy shown in Study AV006 against influenza A/H3N2 and B support the conclusion that FluMist is highly efficacious against all three strains of influenza.

5.3.3. Conclusions

The data for FluMist from both years of the Phase 3 Pediatric Protective Efficacy Trial, Study AV006, confirm previous studies with CAIV in children showing that live, attenuated, cold-adapted influenza vaccine is generally safe, well-tolerated and protective against community-acquired, culture-confirmed influenza. The overall efficacy of FluMist was 92.6% in Year One and 87.1% in Year Two for a combined efficacy of 91.7%. FluMist also was effective in reducing the occurrence of influenza-associated lower respiratory illness, influenza-associated febrile illness, and influenza-associated otitis media in both years of the study. Additionally, in both study years combined, the overall incidences of febrile illness associated with antibiotic use and febrile otitis media associated with antibiotic use were significantly reduced regardless of the influenza culture result in children who received FluMist compared to children who received placebo. Since A/H1N1 did not circulate in the US during the two seasons of Study AV006 in which field efficacy was evaluated, the Pediatric Challenge Trial, Study AV011, was conducted with monovalent Type A/H1N1 vaccine virus. FluMist provided 82.9% protection against viral shedding, which is a surrogate for natural infection with A/H1N1 virus. Furthermore, data from these studies of FluMist are supported by prior efficacy trials of similar CAIV that showed these vaccines to be efficacious in preventing culture-confirmed influenza illness and effective in preventing disease. Thus, FluMist is expected to provide high protective efficacy against all three influenza strains represented in the vaccine.

5.4. Efficacy Conclusions

Data from the pivotal Aviron Studies AV003, AV009, AV006, and AV011 (Table 2), involving 4,653 healthy adults and 1,602 healthy children show that FluMist provides a high degree of protection against influenza in these populations. Specific efficacy and effectiveness conclusions supported by these studies include the following:

Healthy Adults

- FluMist is highly effective in preventing laboratory-documented influenza illness in healthy adults resulting from direct challenge with wild-type influenza A/H1N1 or A/H3N2 or B. It has an overall estimated efficacy of 85% compared to placebo (Study AV003).

- The 85% efficacy of FluMist (95% CI: 28, 100) is similar to the efficacy of 71% (95% CI: 2, 97) of a licensed TIV [Fluvirin] in preventing laboratory-documented influenza illness resulting from direct challenge with influenza Type A/H1N1 or A/H3N2 or influenza B in healthy adults (Study AV003).
- FluMist consistently reduced days of missed work during illnesses (Study AV009)
 - 13.1% (95% CI: -0.9, 25.2) reduction during any febrile illness ($p = 0.065$)
 - 17.9% (95% CI: 4.3, 29.5) reduction during severe febrile illness ($p = 0.012$)
 - 28.4% (95% CI: 16.3, 38.8) reduction during febrile upper respiratory illness ($p < 0.0001$)
 - 19.4% (95% CI: 7.5, 29.7) reduction during upper respiratory illness ($p = 0.0021$)
- FluMist consistently reduced days of health care provider visits during illness (Study AV009)
 - 14.7% (95% CI: -0.3, 27.5) reduction during any febrile illness ($p = 0.0548$)
 - 24.8% (95% CI: 11.6, 36.1) reduction during severe febrile illness ($p = 0.0006$)
 - 40.9% (95% CI: 30.1, 50.0) reduction during febrile upper respiratory illness ($p < 0.0001$)
 - 45.5% (95% CI: 36.8, 53.0) reduction during upper respiratory illness ($p < 0.0001$)
- FluMist was clinically effective in significantly reducing days of illness (Study AV009)
 - 22.9% (95% CI: 12.1, 32.4) reduction in days of any febrile illness ($p = 0.0001$)
 - 27.3% (95% CI: 16.7, 36.5) reduction in days of severe febrile illness ($p < 0.0001$)
 - 24.8% (95% CI: 13.5, 34.7) reduction in days of febrile upper respiratory illness ($p = 0.0001$)
- FluMist was very effective in reducing illness, missed work, and illness associated health-resource utilization in healthy working adults despite the fact that the predominant influenza strain in 1997–1998 was a drifted strain (A/Sydney/05/97[H3N2]) not included in the vaccine (Study AV009).

- FluMist is suitable for routine use in healthy adults. It is expected to have high efficacy against clinical illness and the associated economic impact resulting from natural exposure to all three influenza strains in the vaccine. FluMist offers an option for effectively preventing the manifestations of influenza among healthy, working adults.

Healthy Children

- Among children who received two doses of FluMist in Year One of the Pediatric Protective Efficacy Trial (Study AV006), the estimated vaccine efficacy was 93.4% (95% CI: 87.5, 96.5) in preventing culture-confirmed influenza. Two doses of vaccine also were highly efficacious against the individual strains that circulated in the community, H3N2 (96.0%) and B (90.5%).
- Among children who received one dose of FluMist in Year One of the Pediatric Protective Efficacy Trial (Study AV006), the estimated vaccine efficacy was 88.8% (95% CI: 64.5, 96.5) in preventing culture-confirmed influenza. One dose of vaccine also was highly efficacious against the individual strains that circulated in the community A/H3N2 (86.9%) and B (91.3%).
- Among children who were randomized to receive one or two doses in Year One of Study AV006 (an intent-to-treat analysis), the vaccine efficacy was 92.6% (95% CI: 87.3, 95.7) in preventing culture-confirmed influenza.
- The vaccine efficacy in Year One of Study AV006 was 95.0% (95% CI: 90.0, 97.5) in preventing febrile illness associated with influenza and was 97.5% (95% CI: 85.5, 99.6) in preventing otitis media associated with influenza.
- Among children who received a single re-vaccination of FluMist in Year Two of the Pediatric Protective Efficacy Trial (Study AV006), the estimated vaccine efficacy was:
 - 87.1% (95% CI: 77.7, 92.6) in preventing culture-confirmed influenza;
 - 100% (95% CI: 63.1, 100) in preventing culture-confirmed influenza caused by circulating strains represented in the vaccine;
 - 85.9% (95% CI: 75.3, 91.9) in preventing culture-confirmed influenza caused by a drifted circulating strain not included in the vaccine, that is A/Sydney/05/97 (H3N2).

VRBPAC Briefing Document

- The vaccine efficacy in Year Two of Study AV006 was 89.3% (95% CI: 80.4, 94.2) in preventing febrile illness associated with influenza and 94.3% (95% CI: 78.1, 98.5) in preventing otitis media associated with influenza.
- The vaccine efficacy in AV006 Years One and Two combined was 95.2% (95% CI: 62.2, 99.4) in preventing lower respiratory illness associated with influenza.
- In both study years combined, the vaccine significantly reduced both febrile illness with associated antibiotic use by 23.3%, and febrile otitis media with associated antibiotic use by 30.4% in all randomized children who were ill regardless of viral culture confirmation.
- Participants who received FluMist compared to those who received placebo in Years One and Two of Study AV006, were less likely to shed A/H1N1 vaccine virus after intranasal challenge (Study AV011); efficacy against viral shedding was 82.9% (95% CI: 60.2, 92.7).
- Protection against shedding after A/H1N1 vaccine virus challenge was correlated with pre-existing serum and/or nasal antibody against influenza virus hemagglutinin (Study AV011). However, vaccinees without serum or nasal immune responses were also protected from shedding compared to the placebo group.
- FluMist is suitable for routine use in children and is expected to have high efficacy against illness resulting from natural exposure to all three wild-type influenza strains in the vaccine.