FLUMIST®

Influenza Virus Vaccine Live, Intranasal

2008-2009 FORMULA

SCIENTIFIC PRODUCT MONOGRAPH

AHFS COMPENDIA CLASS—80:12.

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MedImmune
Gaithersburg, MD 20878

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Key Terms

Abbreviations commonly seen in the literature for FluMist®

CAIV: cold-adapted influenza virus

CAIV-T: cold-adapted influenza vaccine, trivalent

CAIV-T, Liquid: new refrigerated formulation of FluMist®

CA: cold-adapted

CR: cold recombinant

LAV: live attenuated virus

LAIV: live attenuated influenza vaccine

Abbreviations commonly seen for injectable influenza vaccine ("flu shot")

IIV: inactivated influenza vaccine

TIV: trivalent inactivated influenza vaccine

Nomenclature Guide to Influenza Virus Strains

Type/	Location of Isolate/	Isolate #/	Year Isolated/	HN Subtype
A/	Brisbane	59/	2007/	(H1N1)
A/	Brisbane	10/	2007/	(H3N2)
B/	Florida	4/	2006/	

[NOTE: The examples shown above are also the representative flu vaccine strains recommended by the CDC for the 2008-2009 season.]

This monograph is being provided in response to requests for full information about FluMist® (Influenza Virus Vaccine Live, Intranasal). It may contain information that is not in the product labeling. This monograph is not intended to offer an opinion on the advisability of administering FluMist® in a manner inconsistent with product labeling. Please refer to the enclosed Prescribing Information (package insert) for FluMist®.

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I. Introduction

Influenza virus, a member of the *Orthomyxoviridae* family of RNA viruses, causes a highly infectious respiratory-tract viral illness ("flu") in persons of all ages. In recurrent winter epidemics, 10% to 20% of the US population is infected, leading to more than 100,000 excess hospitalizations and 20,000 to 40,000 excess deaths annually (36,000 per year in the United States during 1990-1999), principally in the elderly (*CDC/ACIP 2008, Keitel 1998, Simonsen 1997 & 2000, Thompson 2003*). Morbidity and mortality rates are usually much greater during pandemics (*Rennels 2002, Webster 2003*). Indeed, for pandemics of the 20th century (such as those in 1918, 1957, and 1968), influenza attack rates were reported to be as high as 70% (*Neuzil 2001*).

For the year 2005, according to the National Center for Injury Prevention and Control (NCIPC, a division of the Centers for Disease Control and Prevention [CDC]), influenza and pneumonia ranked as the 7th leading cause of death for children 2 to 18 years of age and the 11th leading cause of death for adults 19 to 49 years of age (see *CDC-National Center for Injury Prevention and Control Web site: http://webappa.cdc.gov/sasweb/ncipc/leadcaus10.html*). For vaccine-preventable deaths in the United States, influenza heads the list for both adults (*Ahmed 2001*) and children up to 18 years old (*Bhat 2005*).

Recent CDC-sponsored studies of influenza infection among children found a much higher burden of influenza in the outpatient setting than in the inpatient setting and a lack of clinical recognition (*Poehling 2006*). Few children who had laboratory-confirmed influenza were given a diagnosis of influenza by the treating physician in the inpatient (28%) or outpatient (17%) settings. The CDC has concluded that much of this disease burden may be prevented through vaccination (*CDC/ACIP 2008*).

Pathogenesis, Clinical Features, and Epidemiology

Influenza virus primarily infects the ciliated columnar epithelial cells of the respiratory tract and induces vacuolization, cellular edema, cilial loss, and desquamation. Figure 1 is a photomicrograph of lung pathology in a child with influenza. Loss of the tracheobronchial mucosa, which may be complete or near-complete, is associated with submucosal edema and an inflammatory infiltrate involving both neutrophils and mononuclear cells. Regeneration of the mucosa may take up to a month, thus explaining the persistent cough often experienced by recovering influenza patients (*Playford 2002*).

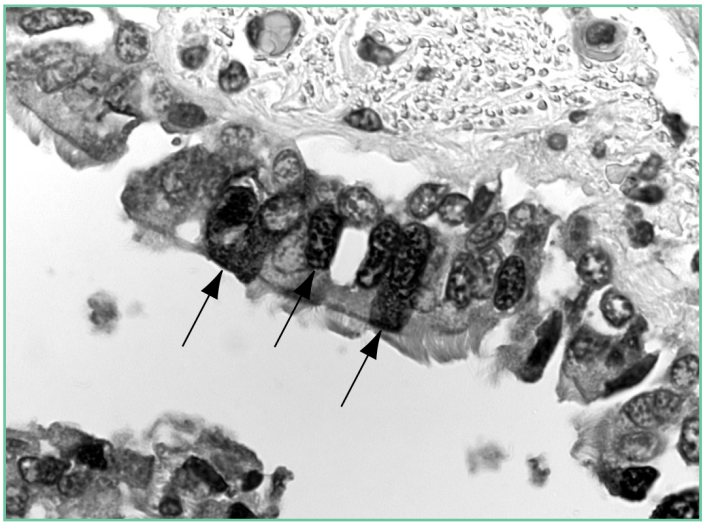

Figure 1.—Influenza A viral antigens (dark areas indicated by arrows), demonstrated by immunohistochemical staining, in ciliated bronchial epithelial cells from a deceased child with influenza A virus infection. (Reprinted from CDC 2003.)

Because they may be immunologically naive to various influenza strains on first exposure, children may be especially vulnerable to influenza.

Children appear to play a pivotal role in secondary transmission of illness to household members and in viral amplification in communities at large.

—Glezen 1982

Spread of influenza viruses is principally by airborne droplets (primarily produced by a cough or sneeze), but also by contact with contaminated items (*CDC/ACIP 2008, Musher 2003*). Environmental survival may exceed 24 hours in droplets and on nonporous surfaces under conditions of low humidity (*Bean 1982, Playford 2002*). Airplane travel, which permits prolonged contact in relative confinement with infected persons, may contribute to the introduction of new virus strains into a community (*Leder 2005, Moser 1979*).

The incubation, or "latent," period (defined as the gap between exposure to the influenza virus and development of symptoms) is 1 to 4 days, with an average of 2 days (*Rennels 2002, US Govt-Homeland Security 2007*). Viral shedding, and the period during which a person may be infectious to others, generally peaks on the second day of symptoms. Children will shed the greatest amount of virus and, therefore, are likely to pose the greatest risk for transmission. Children can be infectious for more than 10 days, and young children can shed virus for up to 6 days before their illness onset. The length of time of viral shedding may be prolonged during initial infection with a new influenza subtype. Severely immunocompromised persons can shed virus for weeks or months (*US Govt-Homeland Security 2007*).

In most persons, influenza is a self-limited but acutely prostrating illness with often severe systemic symptoms (such as fever, chills, profound malaise, myalgias, and headache), as well as respiratory symptoms (including sore throat, rhinitis, and cough) (*Boivin 2000, Monto 2000, Nicholson 1992*). The clinical presentation in children may be more variable than that in adults and the elderly (see Table 1), with nonspecific fever, acute febrile seizures, and gastrointestinal symptoms that can necessitate hospitalization (*Cox 1999, Nicholson 1992*).

Please see accompanying Full Prescribing Information (Package Insert).

Table 1.—Presentation of Clinical Influenza Differs by Age Group[a,b]

Sign/Symptom	Children	Adults	Elderly (> 65 y/o)
Cough (non-productive)	++	++++	+++
Fever (≥102°F)	+++	+++	+
Myalgia	+	+	+
Headache	++	++	+
Malaise	+	+	+++
Sore throat	+	++	+
Rhinitis/nasal congestion	++	++	+
Abdominal pain/diarrhea	+	-	+
Nausea/vomiting	++	-	+

[a] Adapted from Cox and Subbarao 1999 and Monto et al. 2000.
[b] ++++ Most frequent sign/symptom; + least frequent; -infrequent.

Because they may be immunologically naive to various influenza strains on first exposure, children may be especially vulnerable to influenza and its complications. Death associated with laboratory-confirmed influenza virus infection among children (defined as persons age <18 years) is a nationally reportable condition. For example, CDC reports of laboratory-confirmed deaths in children younger than 18 years during the 2003-2004 influenza season (September 28, 2003 to May 22, 2004) indicated that 77% did not have an underlying high-risk medical condition and 47% were healthy prior to death (*Bhat 2005, CDC 2004, Cochi 2004*). While influenza-associated deaths are uncommon among children, an estimated annual average of 92 influenza-related deaths (0.4 deaths per 100,000 persons) occurred among children aged <5 years during the 1990s compared with 32,651 deaths (98.3 per 100,000 persons) among adults aged >65 years (*CDC/ACIP 2008*). The annual number of deaths among children reported to CDC for the past four influenza seasons has ranged from 39 during 2004-2005 to 84 during 2007-2008.

In May 2007, an advisory was issued by the CDC regarding an increase in the number of influenza-associated pediatric deaths and coinfections with *Staphylococcus aureus* during the 2006-2007 season (*CDC 2007*). Of the 68 reported deaths among children associated with influenza infections during the 2006-2007 season, a total of 21 had coinfections with either methicillin-resistant or sensitive *S. aureus*. Compared with the previous two influenza seasons, there has been an increase in proportion with invasive MSRA-associated co-infection from <5% to 27%. The CDC has noted, *"The reason for this increase is not established but might reflect an increasing prevalence within the general population of colonization with MRSA strains, some of which carry certain virulence factors"* (*CDC/ACIP 2008*).

Seasonal epidemics often occur in 2 waves—the first in schoolchildren and their household contacts (generally younger people) and the second mostly in housebound or institutionalized people, particularly the elderly (*Merck Manual online: http://www.merck.com/mmpe/sec14/ch188/ch188d.html*). School absenteeism often precedes work absenteeism in a community (see Figure 2) (*Glezen 1978*).

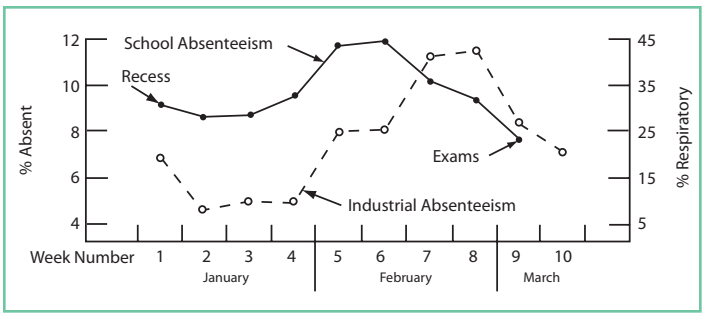

Figure 2.—Relationship of school and industrial absenteeism. (Adapted from Glezen WP and Couch RB. Interpandemic influenza in the Houston area, 1974-76. *N Engl J Med.* 1978;298:587-592. Copyright ©1978 Massachusetts Medical Society. All rights reserved. Adapted with permission, 2004.)

Epidemiological probe analyses suggest that the elderly have the highest mortality rate attributed to influenza, as reflected in seasonal all-cause mortality (*Monto 1996, Nordin 2001, Thompson 2003*). However, the majority of influenza-associated hospitalizations are in children and adults without defined high-risk conditions (for a greater attributable risk), and they comprise a larger proportion of the total population (*Glezen 1987*). Please see Figure 3.

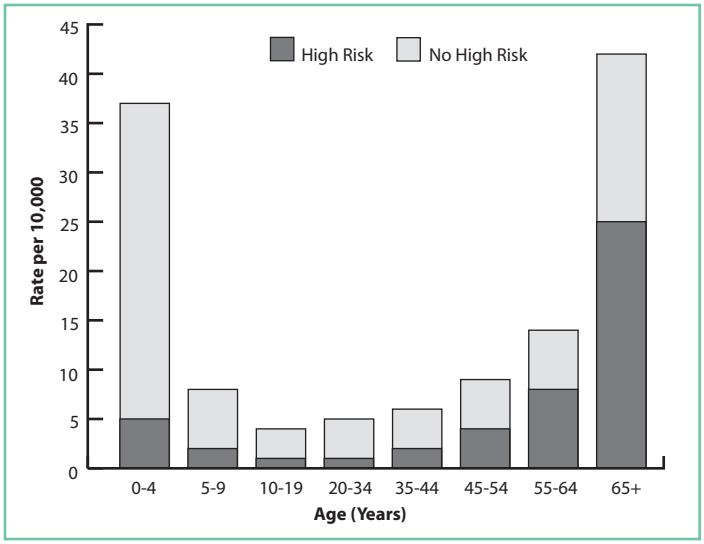

Figure 3.— Acute respiratory disease hospitalizations in influenza epidemics by risk and age, Houston 1978-1981. (Adapted from Glezen et al. 1987.)

Overall, rates of influenza-associated hospitalization are higher among young children (than among older children) when influenza viruses are in circulation and similar to rates for other groups considered at high risk for influenza-related complications, including persons aged >65 years (*CDC/ACIP 2008*). Table 2 shows hospitalization rates from a study of 3 influenza outbreaks from 1978 to 1981.

Table 2.—Hospitalization Rates[a] for Acute Respiratory Disease During 3 Influenza Epidemics (Harris County, Texas)[b]

Age (Years)	Epidemic		
	1980 to 1981	1979 to 1980	1978 to 1979
<1	734	614	505
1 to 4	354	260	267
5 to 9	74	74	62
10 to 24	54	34	50
25 to 44	112	78	64
45 to 54	132	79	68
55 to 64	180	159	89
65+	589	378	304

[a]Per 100,000.
[b]Adapted from Perrotta et al. 1985.

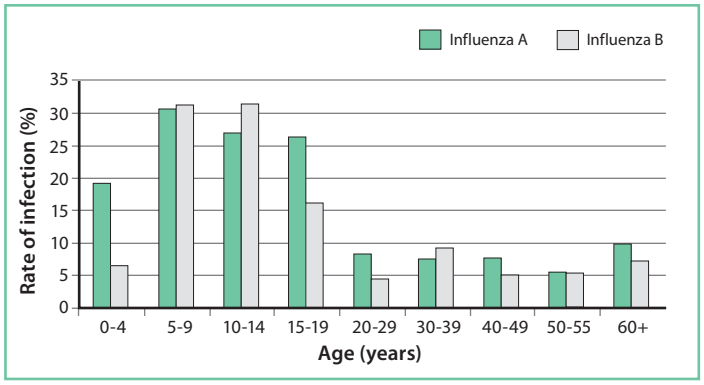

Figure 4A.—Average rates of infection by influenza A and B viruses in different age groups of subjects during several influenza epidemics in Tecumseh, Michigan, USA, 1976-1980. (Data from Monto and Sullivan. Reprinted from Acta Paediatrica, 2006)

Children also appear to play a pivotal role in secondary transmission of illness to household members and in viral amplification in communities at large (*Glezen 1982, Jennings 1978, Taber 1981*) (See Figure 2). Their importance in the propagation of influenza epidemics has been seen in the sequential shift of peak attack rates from children to adults, in the interruption of outbreaks during school holidays, and in reductions in community and staff attack rates with the controlled intervention of school-based vaccination (*Glezen 1982, Monto 1970, Rudenko 1993*). Indeed, influenza infection rates in school-aged children (5- to 15-year-olds) are the highest of any age group (see Figures 4A and 4B) (*Monto 1993, Sullivan 1996, Szucs 1999*). The relatively prolonged interval of viral shedding in infected children (>50% shedding at 6 to 7 days after illness onset) may contribute to their agency in viral transmission (*Frank 1981*).

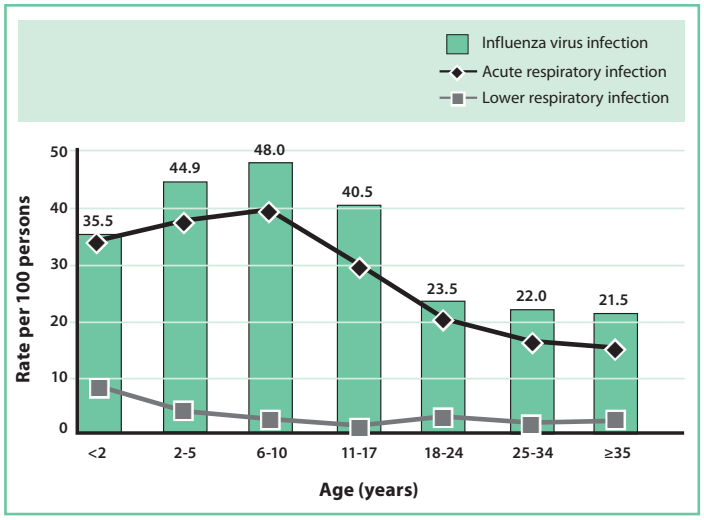

Figure 4B.—Age-specific annual influenza infection rates Houston family study, 1976-1984 (*Glezen 1997*).

Parents missed 1 day of work for every 3 days of influenza-associated illness experienced by their child.

—Neuzil 2002

The direct (provision of care) and indirect (lost productivity) costs of influenza in the United States exceed $87 billion annually according to recent CDC estimates.

—Molinari 2007

Medical and Economic Impact of Influenza

The total medical and economic impact of influenza in healthy adults and children is considerable, with annual attack rates of laboratory-confirmed influenza usually exceeding 10% in adults and 30% in children (*Glezen 1978, Neuzil 2002a, Sullivan 1993*).

School-aged children are infected at over twice the rate of adults, as reflected in incidence rates ranging from 23% to 48%, with associated school absenteeism of 0.8 to 2.25 days per illness episode (*Neuzil 2002b, Sullivan 1996, White 1999*). A prospective survey study (313 children in 216 families) of an elementary school (kindergarten to 8th grade) in Seattle, Washington, during the 2000-2001 flu season reported that parents missed 1 day of work for every 3 days of influenza-associated illness experienced by their child (*Neuzil 2002b*). For every 10 children who missed school for an influenza-associated illness, 8 household members subsequently became ill.

The direct (provision of care) and indirect (lost productivity) costs of influenza in the United States exceed $87 billion annually according to recent CDC estimates (*Dobson 2007, Molinari 2007*). See Figure 5A. Based on US population data for 2003, CDC calculated that 24.7 million cases of influenza occur annually, resulting in 41,008 deaths (610,660 life-years lost) and 334,185 hospital admissions (involving 3.1 million days in hospital). In addition, 31.4 million outpatient visits involving 10.6 million patients were also estimated. Days of lost productivity by age group were charted by the CDC (see Figure 5B).

In comparison, community-acquired pneumonia (CAP) affects approximately 4 million US adults annually, with approximately 20% requiring hospitalization. The financial impact of CAP is reported to be about $9.7 billion per year (*Harrison 2008*).

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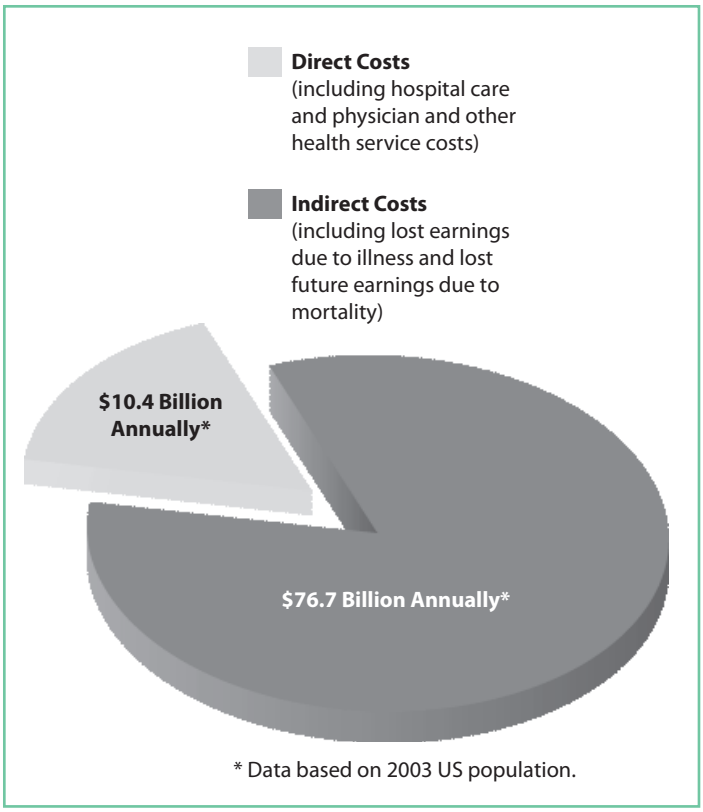

Figure 5A.—The annual CDC-estimated burden of influenza in the USA (Dobson 2007, Molinari 2007).

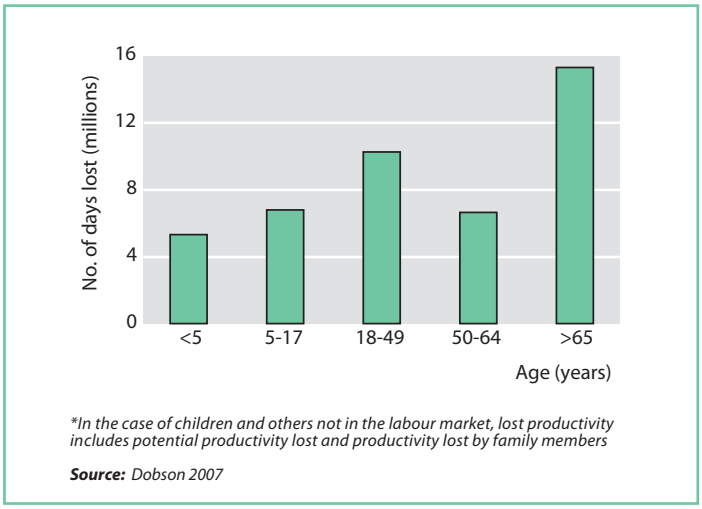

Figure 5B.—Days of productivity* lost by US citizens in 2003 as a result of flu.

Basis for Annual Vaccination

Human influenza viruses (types A and B) are the principal causes of influenza illness (*CDC/ACIP 2008*). Influenza virus A strains are divided into subtypes on the basis of 2 surface antigens, *hemagglutinin* (HA) and *neuraminidase* (NA), while influenza virus B circulates in a single subtype but two distinct genetic lineages (Yamagata and Victoria). Notably, influenza B viruses undergo antigenic drift less rapidly than influenza A viruses.

Continuous mutation of the influenza virus genome—RNA polymerases have an error rate of 10^{-4} to 10^{-5} misincorporations per nucleotide position per genome (*Murphy 2002, Smith 1987*)—leads to an accumulation of genetic and accompanying antigenic changes that results in the evolution of viruses into recognizable antigenic lineages or strains within a subtype. Protective immune responses to HA and possibly NA antigens result in population immunity to circulating strains, but this immune barrier eventually selects for strains that have undergone minor antigenic change (point mutations), or "drift" (see Figure 6). Since these emergent heterosubtypic variants can escape immunity to HA and NA antigens of previously circulating strains, flu vaccines must be updated annually to match the contemporary strains. The US Public Health Service (USPHS) and the World Health Organization (WHO) annually select the strains for influenza vaccines in the United States and internationally, respectively, in response to such changes (*CDC/ACIP 2008*).
For these reasons, annual vaccination against influenza is recommended for optimal protection.

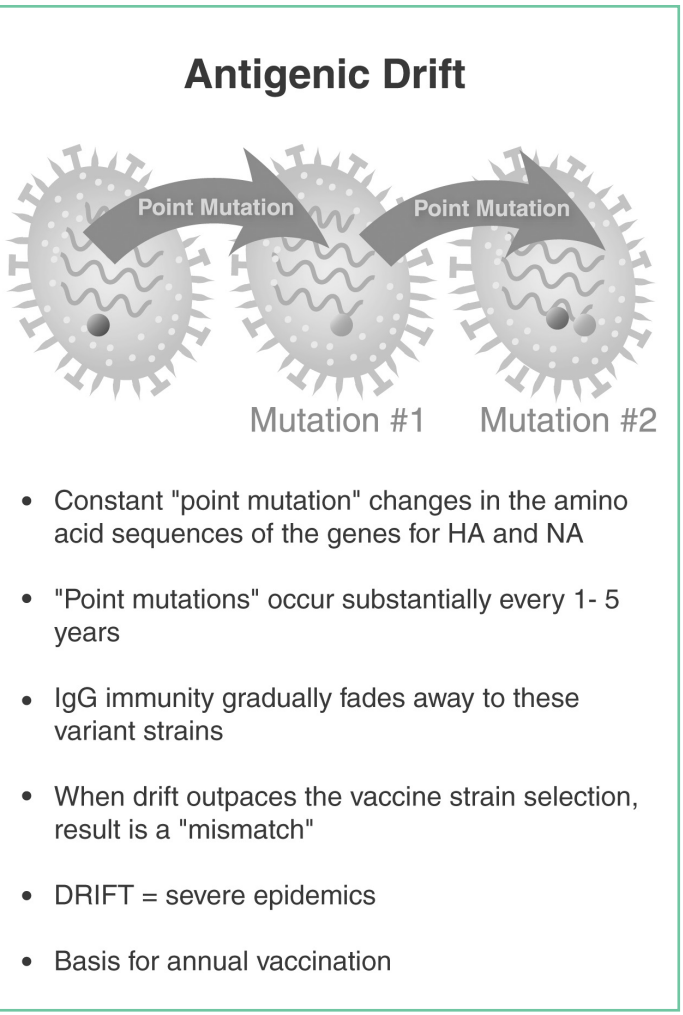

Figure 6.— Antigenic drift.

Herd Immunity With Vaccination of Children

Several studies suggest that increased use of influenza vaccine among children could reduce illness in household or community contacts via herd immunity (*Chowell 2008, Ghendon 2006, Hurwitz 2000, Monto 1970, Piedra 2007, Reichert 2001, Weycker 2003*). In a randomized controlled trial of inactivated influenza vaccine (TIV) for preschool children, unvaccinated household contacts of TIV-vaccinated children had 42% fewer febrile respiratory illnesses compared with unvaccinated household contacts of control children (*Hurwitz 2000*). Mass vaccination of school children resulted in reduced respiratory illness in the

Please see accompanying Full Prescribing Information (Package Insert).

community at large (*Monto 1970*) and, in Japan, reduced influenza-associated mortality rates among both the elderly and children (*Reichert 2001, Sugaya 2005*), confirming that immunization on a large scale can affect community and even national influenza epidemics (*Longini 2000*). Similar findings for FluMist® were observed in herd immunity studies (*King 2005, Piedra 2005a*).

According to a recent simulation model of influenza infection in various "mixing" groups (household, playgroups, and schools), routine influenza vaccination of 60% of US children 1 to 18 years of age would be predicted to reduce the population-wide burden of influenza by 79% to 85% and provide potential savings of $47 and $199, respectively, for direct (excluding cost of vaccination) and indirect costs per vaccinated child (*Weycker 2003*). In a more recent report, it was estimated that the vaccination of 60-100% of healthy individuals 2-64 years of age would be required to interrupt the transmission of influenza in most seasons (*Chowell 2008*).

Vaccine Mismatch Resulting From Antigenic Drift

A "vaccine mismatch" occurs when the annual influenza vaccine contains a strain that is antigenically distinct from the contemporary epidemic strain(s) circulating in the community that season. In the last 12 years, according to CDC data, there were 6 seasons in which there was a mismatch between a circulating strain and 1 of the 3 vaccine strains (see Table 3). It should be noted that the mismatched strain may be virulent but may not dominate the season (>50% of all isolates), as occurred in 2007-2008, 2005-2006, and 2000-2001 seasons. Likewise, it may not cause greater morbidity and mortality that season, but its effect may be noted the next season (*Pyhala 2004*). Recognizing these concerns, recent clinical trials with FluMist® and TIV have assessed efficacy against both matched and mismatched strains.

Table 3.—Mismatched Vaccine and Epidemic Strains of Influenza Over the Past 12 Years in USA*

Influenza Season	Mismatched Influenza Type	Vaccine Strain	Mismatched or "Drifted" Strain	% Drifted in Mismatched Type	Ratio of the Drifted Strain/All Strains Antigenically Characterized (aka % of All Isolates)
2007-2008	A/H3N2 B	A/Wisconsin B/Malaysia	A/Brisbane B/Florida	65% 97%	19% 28%
2005-2006	B	B/Shanghai	B/Victoria	81%	26%
2004-2005	A/H3N2	A/Wyoming	A/California	78%	51%
2003-2004	A/H3N2	A/Panama	A/Fujian	89%	82%
2000-2001	B	B/Bejing	B/Sichuan	89%	40%
1997-1998	A/H3N2	A/Wuhan	A/Sydney	81%	77%

*Each influenza season (October through May), the CDC antigenically characterizes a subset (typically about 5% to 10%) of all positive influenza Type A and B virus specimens collected by U.S. hospitals and laboratories. From this subset are derived the data displayed above. During any given influenza season, emergence of a drift strain (% drifted in mismatched type) can result in a vaccine mismatch. Depending on when the drift strain emerges during the season (e.g., early in the season or late in the season) and whether the drift strain is more or less virulent, the drift strain may or may not be a dominant strain for that season (% of all isolates), as seen in 2007-2008, 2005-2006, and 2000-2001 seasons.

Type A H3N2 and Type B strains tend to show the most drift/lineage variation. If not displayed, it indicates that the vaccine strain matched well that season (<40% drift in mismatched type occurring).

For more details on the CDC surveillance program and list of annual seasonal summaries as referenced above, see Web page: http://www.cdc.gov/flu/weekly/fluactivity.htm

FluMist® (frozen formulation) became the first new influenza vaccine (as well as the first nasally administered vaccine of any kind for human use) in the United States since introduction in the 1940s of injectable trivalent influenza vaccine (TIV).

—Bertino 1997

Vaccination of all children aged 5-18 years is a new ACIP recommendation.

—CDC/ACIP 2008

Please see accompanying Full Prescribing Information (Package Insert).

II. Product Description

FluMist® (frozen formulation) was approved for US marketing on June 17, 2003, and became the first new influenza vaccine—as well as the first nasally administered vaccine of any kind for human use—in the United States since introduction in the 1940s of injectable trivalent influenza vaccine (TIV) (*Bertino 1997, Grabenstein 2006*). It is the culmination of over 40 years of collaborative research and development between inventor Dr. Hunein "John" Maassab (University of Michigan) and scientists from the National Institutes of Health (NIH) and biopharmaceutical industry (Wyeth, Aviron, and MedImmune Vaccines, Inc) (*Newvine 2004*). Categorically, it is often termed in the literature as CAIV-T (cold-adapted influenza vaccine), CR (cold recombinant), LAV (live attenuated virus), or LAIV (live attenuated influenza vaccine) vaccine. The rationale for using cold-adaptation techniques to attenuate influenza viruses was based on earlier success with poliovirus, Japanese B encephalitis virus, and measles virus (*Dubes 1956 & 1957, Hammon 1963, Hozinski 1966*).

FluMist® is indicated in the United States for the active immunization of individuals 2 to 49 years of age against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.

Indicated Population for Influenza Vaccination, Including FluMist®

The Centers for Disease Control & Prevention (CDC) recently stated, *"Vaccination of all children aged 5-18 years is a new ACIP recommendation. In general, health-care providers should begin offering vaccination soon after vaccine becomes available and if possible by October. To avoid missed opportunities for vaccination, providers should offer vaccination during routine health-care visits or during hospitalizations whenever vaccine is available. Vaccination efforts should continue throughout the season, because the duration of the influenza season varies, and influenza might not appear in certain communities until February or March. Providers should offer influenza vaccine routinely, and organized vaccination campaigns should continue throughout the influenza season, including after influenza activity has begun in the community. Vaccine administered in December or later, even if influenza activity has already begun, is likely to be beneficial in the majority of influenza seasons* (*CDC/ACIP 2008*)."

FluMist® is the first nasally administered vaccine available in the United States and offers a needle-free approach to influenza vaccination. FluMist® is indicated for children and adults 2 to 49 years of age (inclusive), including health care workers and persons with close contact to children under 5 years of age and adults ≥50 years old. Please see Table 4. In 2008, the CDC-ACIP recommended that all children 6 months to 18 years of age be given an annual influenza vaccine. These individuals (2 years and older) can receive FluMist® as soon as it becomes available and throughout the season (*CDC/ACIP 2008*). According to CDC data, the addition of 2-17 year olds would add 24.7 million people recommended for annual influenza vaccination.

FluMist® is contraindicated in individuals with a history of hypersensitivity, especially anaphylactic reactions, to eggs, egg proteins, gentamicin, gelatin, or arginine or with life-threatening reactions to previous influenza vaccinations. FluMist® is also contraindicated in children and adolescents (2-17 years of age) receiving aspirin therapy or aspirin-containing therapy, because of the association of Reye's syndrome with aspirin and wild-type influenza infection.

Table 4.— CDC/ACIP Guidelines for 2008-2009 Influenza Season—Updated for Groups Eligible in 2008-2009 Season (2 to 49 Years of Age) for FluMist®

Group*
Any healthy person (2 to 49 years of age, inclusive) who wishes to avoid influenza illness
Health care workers (physicians, nurses, and other personnel in hospital or outpatient care settings, including EMTs, paramedics, etc.)
Students in health-care professions who will have contact with patients.
Nursing home/chronic-care facility employees
Employees of day care centers for children and/or the elderly
Employees of assisted-living residents living at home or in public residences
Any person (family members, friends, etc.) who provides home care to any person(s) in high-risk groups (such as children <5 years old and adults ≥50 years old)
Household contacts (including children ≥2 years of age) of persons in high-risk medical groups
Household contacts (including children ≥2 years of age) of infants and children 0 to 59 months of age
School-aged children (≥2 years of age)

Adapted from CDC/ACIP 2008.

*Inactivated vaccine (TIV) is preferred for people who have close contact with severely immunosuppressed persons (e.g., patients with hematopoietic stem cell transplants) during periods when such persons require care in a protective environment (typically defined as a specialized patient-care area with a positive airflow relative to the corridor, HEPA filtration, and frequent air changes). As a precautionary measure, persons who receive FluMist® should avoid contact with severely immunosuppressed patients for 7 days after vaccination. Hospital visitors who have received FluMist® should avoid contact with severely immunosuppressed persons in protected environments for 7 days after vaccination but should not be restricted from visiting less severely immunosuppressed patients.

Either vaccine (TIV or FluMist®) may be used by health care workers or other persons who have close contact with persons with lesser degrees of immunosuppression (e.g., persons with diabetes, asthmatics taking corticosteroids, persons with HIV, or those patients who previously were in a protective environment) (*CDC/ACIP 2008*).

Product Development

FluMist® is an aqueous nasal spray trivalent formulation of cold-adapted (*ca*), temperature-sensitive (*ts*), attenuated (*att*) live influenza viruses having immunogenic viral coat proteins (hemagglutinin and neuraminidase) from representative wild-type influenza strains. Each of the 3 influenza strains contained in FluMist® is produced by genetic reassortment of a master donor virus (MDV) and a wild-type influenza virus. Two MDVs (A/Ann Arbor/6/60 and B/Ann Arbor/1/66)—1 for the A strain and 1 for the B strain—were developed by Maassab and colleagues (University of Michigan) using serial passage at sequentially lower temperatures in chick kidney cells (*Maassab 1968, 1969, 1972, 1986*). During this process, the 2 MDVs acquired multiple mutations in the 6 internal gene segments that confer the *ca*, *ts*, and *att* phenotypes. The molecular basis of the *ca*, *ts*, and *att* phenotypes has been more accurately studied in recent years by using plasmid-based reverse genetics (*Chen 2006, Jin 2003 & 2004, Kemble 2004a*) (see Table 5).

For each of the 3 influenza strains ("trivalent") contained in FluMist®, the 6 internal gene segments responsible for *ca*, *ts*, and *att* phenotypes are derived from the MDV. The 2 segments that encode the surface glycoproteins, HA and NA, are derived from the antigenically relevant wild-type influenza viruses that have been recommended by the CDC and Food and Drug Administration (FDA) for inclusion in the annual vaccine formulation (*Murphy 2002*). Using a natural reassortant process, coinfection of cells with the MDV and current wild-type strains yields "master virus strains" (MVS) for each of the 3 influenza virus components in FluMist® (see Figure 7). These hybrids are commonly referred to as *6/2 reassortant* vaccine viruses—reflecting the number of RNA segments they inherit from the cold-adapted MDV and wild-type parent viruses, respectively. (Note: The influenza virus genome consists of 8 RNA gene segments.) Starting with the 2008-2009 FluMist® vaccine formula, a plasmid rescue-reverse genetics process replaces the natural reassortant process in order to more rapidly and precisely generate new annual MVS (*Subbarao 2004*).

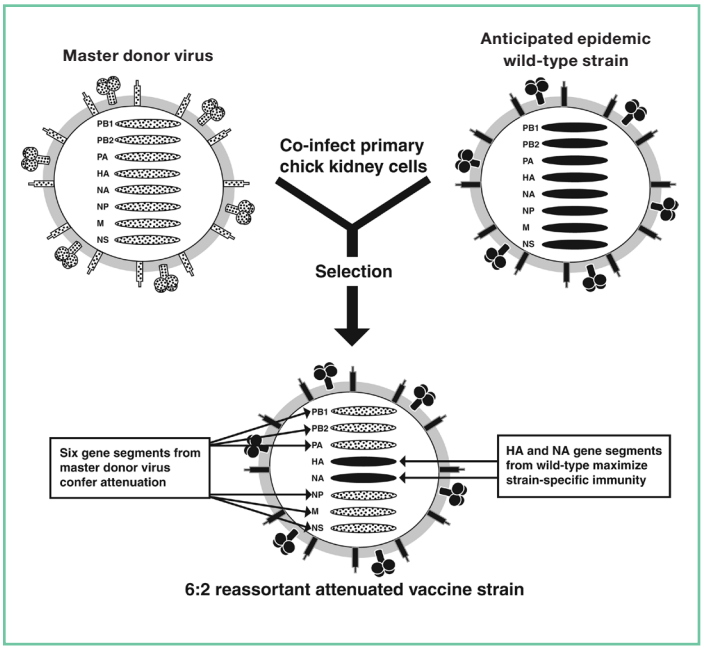

Figure 7.—Derivation of new master virus strain (MVS). In 2008, plasmid-rescue technique replaced co-infect step shown above.

Table 5.—Biological and Genetic Properties of Cold-Adapted Reassortant (CR) Influenza A and B Virus Vaccines[a,b]

		PHENOTYPE		
		Cold Adaptation (*ca*)	**Temperature Sensitivity (*ts*)**	**Attenuation (*att*)**
Gene(s) Associated With Indicated Phenotype	**- FluMist® A Viruses**	PA, PB2 (and possibly 1 other gene)	PB2, PB1, NP	PB1, PB2, NP
	- FluMist® B Viruses	PB2, PB1, NP	PA, NP	PA, NP, M
Characteristics		Efficient growth at 25˚C	Restriction of growth at 37˚C (type B) and 39˚C (type A)	Restricted replication in ferret and human respiratory tract; minimal to no illness produced

[a] Adapted from Keitel 1998 and updated from Chen 2006, Jin 2003 & 2004, and Kemble 2004a & 2004b.
[b] The role of NS gene segment has not been fully elucidated.

FluMist® is completely free of preservatives, including thimerosal and other mercury-containing salts.
—FluMist® Package Insert 2008

An ultra-centrifugation step has allowed for the dose volume to be reduced to 0.2 mL/dose.

The modified vaccine viruses [in FluMist®] replicate primarily in the nasopharynx to initiate immune responses (via mucosal IgA and serum IgG antibodies, and possibly influenza-specific T-cells), but do not replicate well at warmer temperatures found in the lower airways and lung.
—Gruber 2002

By this process, the attenuated strains contained in FluMist® maintain the replication characteristics and phenotypic properties (i.e., cold-adapted, temperature-sensitive, low pathogenicity) of the MDV while expressing the primary antigens, HA and NA, to stimulate immunity to the 3 representative wild-type influenza viruses (A and B strains) that are expected to circulate during the upcoming influenza season (*Belshe 2003*). The molecular basis for FluMist® is what makes it unique from any other influenza vaccine and accounts for its distinct safety and efficacy profile.

Production

After the master virus strains (MVS) are created (via gene reassortment, as described above), they are inoculated into specific pathogen-free (SPF) fertile chicken eggs and incubated to allow for vaccine virus replication. The allantoic fluid of these eggs is then harvested and stabilized with a buffer containing sucrose, potassium phosphate, monosodium phosphate, and monosodium glutamate (MSG) (0.19 mg of MSG per FluMist® dose—well below the level commonly associated with allergic and gastrointestinal adverse reactions) (*FDA 1995*). Two additional stabilizers in refrigerator-stored FluMist® are arginine and acid-hydrolyzed porcine gelatin. See Chapter VII for detailed list of excipient concentrations. This enriched allantoic fluid is purified through clarifying and sterilizing grade filters. Gentamicin sulfate is added early in the manufacturing process to prepare the reassortant viruses, at which time residual gentamicin is present at a calculated concentration of approximately 1 mcg/mL. (Later steps of the manufacturing process do not use gentamicin,

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resulting in a diluted residual concentration in the final product of less than 0.015 mcg/mL [limit of detection of the assay]). An ultra-centrifugation manufacturing step introduced with the refrigerated formula in 2007 permits a lower dosing volume of 0.2 mL and reduces the egg ovalbumin protein content to ≤1.2 mcg/mL (i.e., ≤0.24 mcg per 0.2 mL dose). FluMist® is completely free of preservatives, including thimerosal and other mercury-containing salts.

Virus harvests from the 3 strains are subsequently blended and diluted to desired potency level ($10^{6.5\text{-}7.5}$ FFU per strain) with stabilizing buffers to produce trivalent bulk vaccine. Each lot of viral harvest is tested for *ca*, *ts*, and *att* phenotype preservation (*Buonagurio 2006*) and is also tested extensively by *in vitro* and *in vivo* methods to validate they are free of human or avian origin adventitious agents (e.g., *Mycobacterium tuberculosis* and mycoplasma strains).

The bulk vaccine is then filled into individual intra-nasal spray devices, labeled, and held at -15˚C (+5˚F) or below until shipping to the end-user customer—after which time it is only stored in a refrigerator (2˚-8˚C/35˚-46˚F). The final product is produced to standards of "microbiological purity" (United States Pharmacopoeia, 24th edition), but is not sterile for injection (as per TIV vaccine), as it is delivered to the nonsterile surface of nasal mucosa.

Pharmacology, Biostability, and Immunogenicity

Each 0.2 mL dose of FluMist® is formulated to contain $10^{6.5\text{-}7.5}$ FFU (fluorescent focus units) of each of the 3 influenza virus strains recommended by the USPHS for the current influenza season (*CDC/ACIP 2004, Murphy 2002*). These strains are:

(a) *antigenically representative* of influenza viruses that are expected to circulate in humans during the influenza season;

(b) *cold-adapted (ca)*—that is, they replicate efficiently at 25˚C, a temperature that is restrictive for replication of many wild-type viruses;

(c) *temperature-sensitive (ts)*—that is, they are highly restricted in replication at 37˚C (type B strains) or 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 in ferrets (test model) or humans.

The cumulative effect of these changes is that the modified viruses replicate primarily in the naso-pharynx to initiate immune responses (via mucosal IgA and serum IgG antibodies, and possibly influenza-specific T-cells), but do not replicate well at warmer temperatures found in the lower airways and lung (*FluMist® Package Insert 2008, Gruber 2002, Murphy 2002*). In this manner, FluMist® stimulates active immunity to help protect the vaccinee against manifestations of severe influenza illness (*Murphy 2002, Ray 2004, Selin 2004, Topham 2004*). Please see Figures 8A and 8B.

In young children, antibodies persisted for 5 to 8 months after vaccination, and protection generally persisted for at least 1 year.

—Murphy 2002, Zangwill 2003

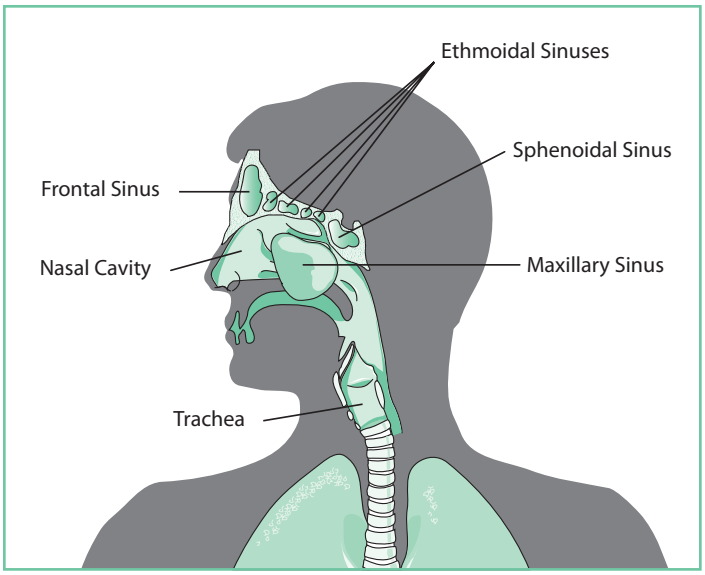

Figure 8A.— IgA antibody and mucosal immunity. This figure shows the upper respiratory tract, where IgA is the dominant antibody. Stimulating mucosal IgA with an intranasal vaccine is advantageous because IgA is secreted at the site of viral replication. FluMist® stimulates mucosal immunity in the upper respiratory tract (*Ghendon 1990, Gruber 2002, Johnson 1986*).

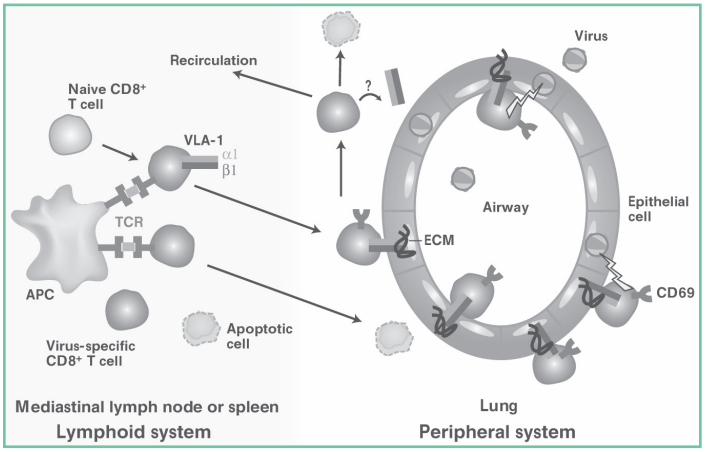

Figure 8B.— Proposed mechanism for T-cell immunity and influenza. These cells are readily available as a first line of defense against reinfection. APC = antigen presenting cell; TCR = T cell receptor; VLA = very long acting adhesion molecule; ECM = extracellular matrix.
(Reprinted with permission from Selin and Cornberg 2004.)

The *attenuation* (measured by influenza-like illness symptoms) and limited *replication* (measured by peak titer of virus in nasopharyngeal secretions) are the major biologic/pharmacologic hallmarks of FluMist®. Wild-type influenza virus replicates at 100- to 1000-fold higher peak titer compared with the cold-adapted influenza virus used in FluMist® (*Murphy 2002*). Please see Figure 9.

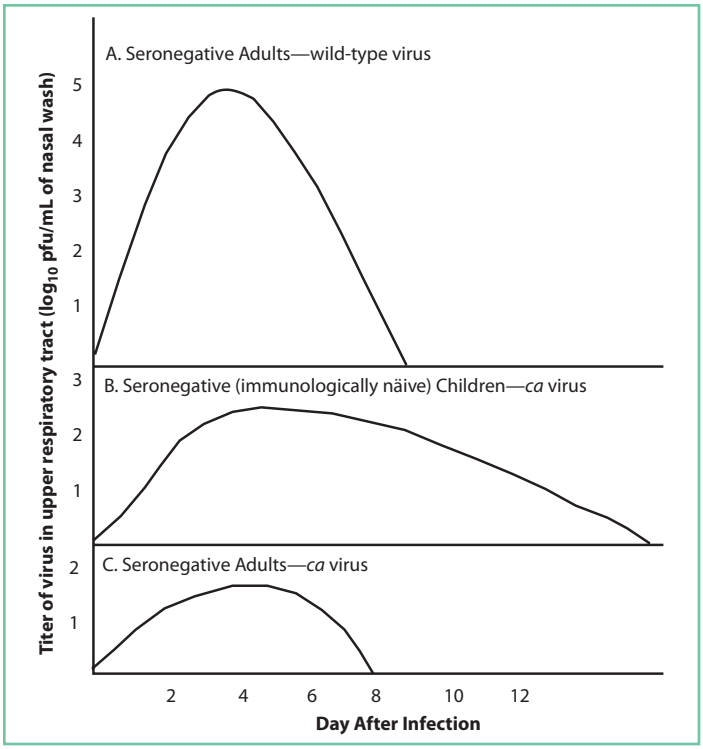

Figure 9.—Level of replication of wild-type versus cold-adapted influenza virus. (A) Level of replication of wild-type influenza A virus in the upper respiratory tract of adults is indicated. The level of replication of the *ca* influenza virus in seronegative infants and children not previously infected with an influenza A virus is indicated (B), and that in seronegative but previously infected adults (C). (Reprinted with permission from Murphy and Coelingh 2002.)

This reduced replication profile has also been demonstrated with several influenza virus strains that were attenuated for use in other CAIV formulations studied in the past. Please see Table 6.

Table 6.—The Level of Attenuation and Replication of Influenza A Wild-Type (*wt*) and 6/2 *ca* Reassortant Viruses in Seronegative Adults[a] (Serum HAI[b] Antibody Titer ≤1:8)

ca reassortant virus	*Influenza A virus subtype*	Percentage of volunteers with febrile or flu-like illness after infection with indicated virus		Mean peak titer of virus (log_{10} $TCID_{50}$/mL NP[c] specimen)	
		wt[d]	*ca*[e]	*wt*	*ca*
A/Alaska/77	H3N2	50	10	4.5	1.0
A/Washington/80	H3N2	46	3	3.6	0.6
A/Korea/82	H3N2	36	0	3.4	0.7
A/Bethesda/85	H3N2	30	9	4.1	0.7
A/Hong Kong/77	H1N1	83	0	6.3	2.6
A/California/78	H1N1	56	4	3.9	1.2
A/Texas/85	H1N1	39	9	3.1	1.8

[a]Reprinted with permission from Murphy and Coelingh 2002.
[b]Hemagglutination inhibiting.
[c]NP, nasopharyngeal wash.
[d]Illness includes, in large part, febrile and systemic symptoms.
[e]Illness is predominantly upper respiratory tract symptoms.

In studies performed to date, viruses shed from vaccinees consistently have been phenotypically and genotypically stable, remaining cold-adapted, temperature-sensitive, and attenuated, with no reversion to virulence detected (*Cha 2000, Vesikari 2006b*).

It is highly improbable for the FluMist® strains to revert to the wild-type influenza virus ("reversion to virulence") phenotype because at least 5 genetic loci on each vaccine strain account for the *ca*, *ts*, and *att* phenotypes. Loss of attenuation in the FluMist® vaccine would require changes in all of these mutations concurrently (*Kemble 2004a & 2004b, Murphy 2002*). Given the error rate of 10^{-4} to 10^{-5} misincorporations per nucleotide position per genome during replication (*Murphy 2002, Smith 1987*),

In 48 completed clinical research trials worldwide, more than 48,000 subjects ranging in age from 6 weeks to >90 years received frozen or refrigerated formulations of FluMist®.

The clinical benefit of FluMist® was studied for 2 broadly distinct endpoints: *efficacy* and *effectiveness*.

which is even slower for B-strains (*Nobusawa 2006*), the odds for a FluMist® virus particle to revert to wildtype influenza would be at least 1×10^{20} replication cycles (which time-wise is over a millenia, as 1 replication cycle in humans occurs approximately every 6 hours) (*Kamps 2006*).

The immunogenicity of 19 different CAIV strains was studied over a period of 25 years at various investigative sites and in different populations (*Murphy 2002*). The serum antibody response (e.g., IgG) elicited is characteristic of a primary viral infection (*Keitel 1998*). Protection against influenza correlates (although imperfectly) with serum IgG hemagglutination-inhibiting antibodies (HAI), especially in seronegative children. (Most studies of correlates of immune protection against influenza have focused on serum HAI antibody.) After 2 doses of CAIV, serosusceptible children mounted an adequate HAI response (>90% seroconverted to type A/H3 and B strains, and 60% to 90% to type A/H1 strain) (*Belshe 1998 & 2000a, Zangwill 2003*). Antibodies persisted for 5 to 8 months after vaccination with CAIV, and protection generally persisted for at least 1 year (*Zangwill 2003*). Protective efficacy has been demonstrated to last for the duration of the influenza season and as late as 5.5 to 13 months after the first dose (*Ambrose 2008, Tam 2007*). In adults, the serologic response has been less robust (<35% for A/H3 and B, and 60% to 90% for A/H1), and the correlates of immunity may be related to other immune responses (*Gorse 1995, Tomoda 1995, Zangwill 2003*). (Note: Immune mechanisms conferring protection against influenza after administration of FluMist® vaccine, as in natural influenza, are not fully understood.) CAIV may be more effective than TIV in inducing a nasal IgA response, while TIV vaccine more consistently elicits serum HA antibodies in adults (*Beyer 2002, Cox 2004*).

Please see accompanying Full Prescribing Information (Package Insert).

III. Clinical Development Trials

FluMist® (trivalent formulation) is licensed in the United States for active immunization and prevention of disease caused by influenza A and B viruses in children, adolescents, and adults 2 to 49 years of age (inclusive). The studies described in this chapter include all subjects enrolled in the worldwide clinical development trials and, as such, include some data that are not within the currently approved age range for FluMist® administration.

Study data were submitted to FDA (Food & Drug Administration) in 3 different BLAs (Biological License Applications), which resulted in the initial frozen formulation approval in 2003 (indicated for ages 5-49 years), and 2 approvals in 2007 covering the refrigerated formulation and expanded indication for children 2-5 years of age.

In 48 completed clinical research trials worldwide, more than 48,000 people ranging in age from 6 weeks to >90 years received frozen or refrigerated formulations of FluMist®. Please see Tables 7 and 8. More than 40,000 children and adolescents from 6 weeks to 18 years of age, including >2000 with conditions such as asthma, recurrent respiratory tract illness, or human immunodeficiency virus (HIV) infection, received at least 1 dose of FluMist® in these clinical trials.

In addition to this clinical trial experience, more than 45,000 doses of frozen FluMist® have been administered in 2 post-marketing safety studies, and approximately 10 million doses have been distributed for commercial use following the initial US licensure in 2003 and up through 2007-2008 season. Refrigerated FluMist® formulation was licensed in 2007 and replaced the frozen formulation product.

Efficacy and Effectiveness Study Endpoints

One or more approaches are typically used in clinical trials to assess the benefit of an influenza vaccine: 1) comparison of culture-positive influenza infection rates (the "gold standard"), 2) a 4-fold antibody increase from baseline levels during the influenza epidemic (serology), or 3) observations of clinical events (e.g., influenza-like illnesses [ILI] or "medically attended acute respiratory illness" [MAARI]) (categorically termed "effectiveness"). Trials with culture-positive endpoints are most feasible in young children because they readily shed influenza virus. Adults shed virus in low quantity and for shorter duration, thus adult trials are more commonly conducted using clinical event endpoints (*Belshe 2004*). Serology assessments are subject to inherent bias from prior vaccine or natural disease exposure, and thus this method has limited research value with older subjects. Serology still endures as a standard assessment for injectable TIV vaccine ("flu shot").

The clinical benefit of FluMist® for licensure was studied for 2 distinct endpoints: *efficacy* and *effectiveness*.These study endpoint categories were defined as follows:

Efficacy—protection of FluMist® against culture-confirmed and/or serologically confirmed influenza.

Effectiveness—reduction in influenza-like illness-associated morbidity (e.g., febrile illnesses), work or school absenteeism, health care utilization (e.g., doctor visits, hospitalizations), incidence of otitis media, and antibiotic use during a known or suspected influenza season.

Efficacy studies were performed primarily in children and adolescents, as noted in Tables 7 and 8. Protective efficacy of FluMist® compared with placebo against culture-positive symptomatic influenza illness caused by matched strains (the primary endpoint of the studies) ranged from 62% to 93% (see Table 9).

Table 7.— Summary of Clinical Development Trials With Frozen FluMist® (formulation marketed 2003-2006)[a]

Pediatric Trials—Frozen FluMist®							
Protocol Number and Publication	**Development Phase**	**Study Goal/ Comments**	**Age Range**	**Total Enrollment**	**FluMist® (frozen)**	**Placebo (or comparator)**	**Key Finding**
AV002 King 1998	I/II	Dose escalation	18-71 months	238	155	83	Seroconversion rates to Type A/H3 & B strains were higher than placebo for all doses except A/H3 at dose of 10^4 $TCID_{50}$. No seroconversion for A/H1 for any dose $<10^7$ $TCID_{50}$.
AV002-2 King 1998	II	Comparison of nose drops and nasal sprayer delivery systems	18-71 months	118	79	39	No differences in HAI responses observed at any dose between recipients who received drops or spray.
AV006 Belshe 1998 Belshe & Gruber 2000 Belshe 2000a Bernstein 2003 Boyce 2000 Mendelman 2001 Piedra 2002a	III Pivotal	Efficacy against culture confirmed influenza, "The Pediatric Efficacy Study"	15-71 months	Year 1: 1602 Year 2: 1858	1070 917	532 441	93% vaccine efficacy (VE) against culture-confirmed influenza. 89% VE after dose 1 and 94% VE after dose 2. No difference in adverse event rates between placebo and FluMist®.
AV007 Zangwill 2001	III Pivotal (manufacturing)	Lot consistency study of FluMist® production for commercial and clinical trial supplies	12-36 months	500	400	100	Commercial production lots were similar with regard to immunogenicity and adverse effects compared with a FluMist® lot used in earlier clinical trial.
AV010 Redding 2002	II/III	Safety in asthmatics	9-17 years	48	24	24	No significant change in % change in FEV1 between FluMist® (0.2%) and placebo (0.4%), p=0.78.
AV011 Belshe 2000b	III	Challenge of subset of AV006 subjects with vaccine strain H1N1 (conducted 20 months after entry; 6-8 months after last FluMist® dose)	34-91 months	222	144	78 (prior)	FluMist® was 83% effective at preventing shedding of H1N1 vaccine virus after challenge.
AV012 Gaglani 2004 Piedra 1999 Piedra 2002b	III	Effectiveness and long-term safety (Herd Immunity Trial)	18 months-18 years	Year 1: 4298 Year 2: 5251[b]	4298 5251	—	20-30% reduction in medically attended acute respiratory illness (MAARI) during A/H1 epidemic.
AV014 Nolan 2003	III Pivotal (manufacturing)	Consistency from 2 manufacturing facilities	12-42 months	225	225	—	FluMist® blended and filled in 2 different facilities had equivalent safety and immunogenicity profiles.
AV015/AV017 Piedra 2002a	III	Safety of revaccination in 3 post-vaccination years of subset of AV006 study population	3-8 years	949	949	—	Mild respiratory, GI, and systemic symptoms of short duration observed in a minority of children after first dose. Sequential annual doses well tolerated.
AV018 Nolan 2008	III	Immunogenicity of concurrent immunization with FluMist® and live MMR and/or varicella vaccines	12-15 months	1245	412	422 (FluMist® + MMR + varicella) 411 (placebo)	No interference between FluMist® and these vaccines.

[a] As of July 2007; parts of some study protocols were published in different articles. Not all studies were included in BLA (Biological Licensing Application) submissions.

[b] Children and adults participated in this protocol.

HAI = hemagglutination-inhibiting antibody assay; MMR = measles, mumps and rubella vaccine; TIV = trivalent inactivated influenza vaccine ("flu shot").

Table 7.—Summary of Clinical Development Trials With Frozen FluMist® (formulation marketed 2003-2006)[a] (cont)

Protocol Number and Publication	Development Phase	Study Goal/ Comments	Age Range	Total Enrollment	FluMist® (frozen)	Placebo (or comparator)	Key Finding
Pediatric Trials—Frozen FluMist® (cont)							
AV019 Black 2002 Bergen 2004	III Pivotal	Safety assessment in Northern California Kaiser Permanente	1-17 years	9689	6473	3216	Asthma signal event observed in children 12-59 months old.
AR001[b] (unpublished)	III	Safety of classical vs. recombinant processes for preparation of FluMist®	<18 years old	18	18	—	FluMist® made by either technique was well tolerated with no differences in adverse effects.
D145-P500 Vesikari 2006b	II/III	Transmissibility of FluMist® in day care setting "The Finnish Daycare Study"	8-36 months	197	98	99	Vaccine strain shedding common, but transmission rate low (0.58% to 2.4%) and without causing influenza illness.
DMID #99-012 King 2001	II	Safety in HIV-infected compared with HIV-negative children	1-7 years old	49 Infected: 24 Negative: 25	49 (crossover)	49	No adverse effects on HIV viral load or CD4 counts after FluMist® compared with placebo.
Adult Trials—Frozen FluMist®							
AV001 (unpublished)	I	Phase I/II spray vs. drops	18-65 years	239	181	58	Immune response was similar after delivery of nasal spray or drops.
AV003 Treanor 2000	III Pivotal	Efficacy against investigational challenge with wild-type influenza	18-40 years	103, 92 challenged	36 (TIV=33)	34	Compared with placebo, FluMist® overall efficacy was 85% and TIV efficacy was 71%. Statistically significant benefit was seen for nasal IgA mucosal antibody against A/H3N2 strain.
AV004 (unpublished)	II	Safety	18-65 years	20	15	5	FluMist® was safe and well tolerated in adults 18-64 years of age.
AV008 Jackson 1999	II/III	Safety in elderly, high risk	≥65 years	200	100 (concomitant with TIV)	100 (placebo + TIV)	Sore throat more common in FluMist® than placebo recipients. No other reactogenicity symptoms associated with FluMist®.
AV009 Mendelman 2001 Nichol 1999 Nichol 2003	III Pivotal	Safety and effectiveness in healthy adults Cost-benefit analysis "The Adult Effectiveness Study"	18-64 years	4561	3041	1520	LAIV reduced severe febrile illness, febrile URI, days of lost work, health care provider visits, use of antibiotics and OTC medications. LAIV patients more likely to experience runny nose and sore throat.
AR001[b] (unpublished)	III	Safety of classical vs. recombinant processes for preparation of FluMist®	≥18 years old	384	384	—	FluMist® made by either technique was well tolerated with no differences in adverse effects.
DMID #98-005 King 2000	II	Safety in HIV-infected compared with HIV-negative adults	18-58 years	111 Infected: 57 Negative: 54	55	56	No adverse effects on HIV viral load or CD4 counts after FluMist® compared with placebo.

[a] As of July 2007; parts of some study protocols were published in different articles. Not all studies were included in BLA (Biological Licensing Application) submissions.

[b] Children and adults participated in this protocol.

HAI = hemagglutination-inhibiting antibody assay; MMR = measles, mumps and rubella vaccine; TIV = trivalent inactivated influenza vaccine ("flu shot").

Table 8.— Summary of Clinical Development Trials With Refrigerated FluMist® (formulation marketed in 2007)[a]

Pediatric Trials—Refrigerated FluMist®							
Protocol Number and Publication	**Development Phase**	**Study Goal/ Comments**	**Age Range**	**Total Enrollment**	**FluMist® (refrigerated)**	**Placebo (or comparator)**	**Key Finding**
MI-CP111 Belshe 2007	III Pivotal	Relative safety and efficacy vs. TIV ("flu shot") "CAIV-T Comparative Efficacy Trial"	6-59 months	8475	4243	4232 (TIV)	FluMist® 54.9% relative efficacy vs. TIV (all strains combined). No medically significant wheezing risk in children ≥2 years old. Increased hospitalizations and risk of wheezing post-vaccination in children <2 years old.
MI-CP112[b] Block 2007	III Pivotal	Frozen vs. refrigerated FluMist® immunogenicity and safety	5-49 years	980	490	490 (frozen FluMist®)	Serum antibody responses, reactogenicity, and adverse event rates all similar for both formulations.
MI-CP123 Belshe 2006	III (follow-up subset of MI-CP111)	Comparative immunogenicity of FluMist® and TIV to matched and mismatched vaccine strains	6-35 months	52	24	28 (TIV)	HAI antibody levels significantly higher for FluMist®.
D153-P002	II	Evaluate immune responses and safety/ tolerability	6-35 months	173	86	43 (placebo) 44 (TIV)	Seroconversion rates were greatest for the A/H3N2 strains and were higher among seronegative subjects compared with all subjects. Reactogenicity events consistent with events in other clinical trials.
D153-P005	II	Vaccine virus shedding evaluation	6-17 months	50	22	28	All subjects shed A/H1 and A/H3 after dose 1 and at lower levels after dose 2 based on culture results. Some recipients shed type B after dose 1, and more subjects shed type B after dose 2.
D153-P500	II	Frozen vs. refrigerated FluMist® immunogenicity and safety	12-35 months	1395	697	698 (frozen FluMist®)	Immunogenicity and reactogenicity events similar between frozen and liquid formulations.
D153-P501 Tam 2007	III Pivotal	Efficacy against culture-confirmed influenza over 2 years; HAI strain-specific immunogenicity	12-35 months	Year 1: 3174 Year 2: 2947	1900 1477	1274 1470	73% efficacy in year 1 and 84% in year 2 (56% for those vaccinated in year 1 but not in year 2).
D153-P502 Vesikari 2006c	III	2-year efficacy and safety in children attending day care	6-35 months	Year 1: 1784 Year 2: 1119	1059 658	725 461	85.9% efficacy in year 1 and 88.7% in year 2. Runny nose/nasal discharge after dose 1 in year 1 was only reactogenicity event significantly more frequent with FluMist® (82%) than placebo (75%) (p=0.001).
D153-P503	II	Determine age of children between 6 and 17 years for which 2 doses of FluMist® conferred an advantage over 1 dose.	6-17 years	498	498	0	A second dose was associated with increase in seroconversion; unknown if this correlates with protective efficacy.
D153-P504 Neto 2008	III	2-year efficacy trial of 2 dose vs. 1 dose in year 1, followed by 1 dose in year 2. Tolerability of gelatin excipient	6-35 months	Year 1: 3200 Year 2: 2202	2131 67	1069 735	Year 1: 1-dose group efficacy 57.7%, 2-dose group efficacy 73.5% against antigenically similar strains. Year 2: 1-dose group efficacy 65.2%, 2-dose group efficacy 73.6% against antigenically similar strains. Gelatin excipient had no impact on reactogenicity or adverse events.
D153-P511	III	Immunogenicity of concurrent immunization with FluMist® and oral polio vaccine (OPV)	12-35 months	2503	835	836 (placebo + OPV) 832 (FluMist® + OPV)	No interference between FluMist® and oral polio vaccine.

[a] As of July 2007; parts of some study protocols were published in different articles. Not all studies were included in BLA (Biological Licensing Application) submissions.

[b] Children and adults participated in this protocol.

HAI = hemagglutination-inhibiting antibody assay; MMR = measles, mumps and rubella vaccine; TIV = trivalent inactivated influenza vaccine ("flu shot").

Table 8.— Summary of Clinical Development Trials With Refrigerated FluMist® (formulation marketed in 2007)[a] (cont)

Protocol Number and Publication	Development Phase	Study Goal/ Comments	Age Range	Total Enrollment	FluMist® (refrigerated)	Placebo (or comparator)	Key Finding
Pediatric Trials—Refrigerated FluMist® (cont)							
D153-P513 Forrest 2008	III	Dose-ranging efficacy trial of 3 different potencies (10^5, 10^6, and 10^7 FFU)	6-35 months	2172	1635	537	Two doses of CAIV-T 10^7 associated with 62.2% efficacy. Two doses of CAIV-T 10^6 associated with 34.7% efficacy, which was not statistically significant. CAIV-T 10^5 failed to demonstrate efficacy.
D153-P514 Ashkenazi 2006	III	Efficacy and safety vs. TIV in children with recurrent RTI	6-72 months	2187	1107	1080 (TIV)	FluMist® 52.7% relative efficacy vs. TIV. No increase in asthma/ wheezing.
D153-P515 Fleming 2006	III	Efficacy and safety vs. TIV in children with asthma	6-17 years	2229	1114	1115 (TIV)	FluMist® 34.7% relative efficacy vs. TIV. No significant increase in asthma/wheezing exacerbation.
D153-P518 Vesikari 2006a & 2008	I	Safety and tolerability in very young infants	6-23 weeks	120	61	59	No adverse effect rate difference from placebo.
D153-P522	III	Immunogenicity of MMR vaccine and efficacy of FluMist® administered concomitantly	11-23 months	1233	819 (+ MMR)	414 (MMR + placebo)	Rubella antibody response lower but within clinically acceptable range.
D153-P526	II	Safety, specifically fever rates	6-17 years	240	118	122	No statistically significant difference in fever rates from placebo
Adult Trials—Refrigerated FluMist®							
D153-P001	II	Evaluate immune responses and safety/tolerability	Adults	20	10	10	IgA response was inconsistent or poorly distinguishable from placebo.
D153-P003	II	Evaluate immune responses and safety/tolerability	18-60+ years	262	131	65 (placebo) 66 (TIV)	Immune response as measured by HAI assay decreased with age. ELISpot assay for gamma-interferon appeared promising as a marker of response. Adverse events were uncommon.
D153-P004	II	Kinetics of the immune response generated by influenza vaccines	18-65 years	31	10	10 (placebo) 11 (TIV)	IgA response was inconsistent or poorly distinguishable from placebo. HAI is a reliable but incomplete marker.
D153-P507 de Villiers 2003	III	Efficacy and safety/tolerability	60-97 years	3242	1620	1622	FluMist® 42.3% efficacy against matched strains. FluMist® group experienced a higher rate of mild influenza-like systemic symptoms after vaccination compared with placebo group.
D153-P510	II	Evaluate immune responses and safety/tolerability	18-60+ years	102	51	51	Single dose was well tolerated and generated an immune response.
D153-P516	III	Relative efficacy vs. TIV against culture-confirmed influenza	≥60 years	3009	1508	1501 (TIV)	Very few cases detected: FluMist® (0.8%) and TIV (0.5%). FluMist® was well tolerated.
D153-P800	I	Safety and tolerability in healthy Japanese males	18-45 years	45	30	15	FluMist® was well tolerated.

[a] As of July 2007; parts of some study protocols were published in different articles. Not all studies were included in BLA (Biological Licensing Application) submissions.

[b] Children and adults participated in this protocol.

HAI = hemagglutination-inhibiting antibody assay; MMR = measles, mumps and rubella vaccine; TIV = trivalent inactivated influenza vaccine ("flu shot").

In one of the largest field efficacy trials (MI-CP111), FluMist® was more efficacious overall than inactivated trivalent influenza injection (TIV, aka "flu shots") in children 6-59 months of age.
—Belshe 2007

In the largest field efficacy trial (MI-CP111), FluMist® was more efficacious overall than inactivated trivalent influenza injection (TIV, aka "flu shots") in children 6 to 59 months of age. In the other large pediatric trial (AV006), the spectrum of illness was milder among the few children in the FluMist® group who had influenza (than in the control group) (*Belshe 2000a*).

Overall, 5 studies can be considered "pivotal" for *clinical benefit* (trial protocols CP111, D153-P501, AV003, AV006, and AV009), and 2 studies were considered "pivotal" for *product manufacturing quality* (trial protocols AV007 and AV014) (see Tables 7 and 8). Comparative immunogenicity and safety were demonstrated for the frozen and refrigerated formulations of FluMist® in 1 pivotal clinical trial (CP112). See Table 8 for details on this bridging/ product equivalency trial. Study protocols AV019 (*Bergen 2004, Black 2002*) and CP111 (*Belshe 2007*) were considered "pivotal" trials for *safety* assessment and are discussed further in Chapter IV (Clinical Safety and Tolerability).

The pivotal clinical benefit studies are reviewed in the text of this chapter, with an analysis of the data for all patients enrolled. They are also selectively described in the FluMist® package insert.

Table 9.—Efficacy of FluMist® Compared With Placebo in Children[a]

Study (Protocol #)	Age[b] (months)	Total Subjects	Number of Doses	Study Season	Efficacy (95% CI)	
					Vaccine-Matched Strains	Overall (matched and mismatched strains)
AV006	15-71	1259[c]	2	1996-1997	**93%** (88, 97)	**93%** (88, 97)
		1110[c]	1	1997-1998	**100%** (54, 100)	**87%** (77, 93)
D153-P501	12-35	2764	2	2000-2001	**73%** (63, 81)	**70%** (61, 77)
		1265[d]	1	2001-2002	**84%** (70, 92)	**64%** (44, 77)
D153-P502	6-35	1616	2	2000-2001	**85%** (74, 92)	**86%** (76, 92)
		1090	1	2001-2002	**89%** (82, 93)	**86%** (79, 91)
D153-P504	6-35	1886[c]	2	2001	**74%** (64, 81)	**72%** (62, 80)
		680[c]	1	2002	**74%** (33, 91)	**47%** (15, 67)
D153-P513	6-35	1041	2	2002	**62%** (44, 75)	**49%** (29, 63)
D153-P522	11-23	1150	2	2002-2003	**78%** (51, 91)	**64%** (36, 80)

[a] All subjects were vaccine-naïve at initial enrollment.
[b] Age at first vaccination.
[c] Includes only subjects who received 2 doses of study vaccine or placebo in year 1.
[d] Includes only subjects who received the same study vaccine in each year of the study.

Please see accompanying Full Prescribing Information (Package Insert).

Efficacy in Children

Study AV006—US Pediatric Efficacy

AV006 was a pivotal, Phase 3, multicenter, randomized, double-blind, placebo-controlled trial performed in US children without high-risk underlying medical conditions to evaluate the efficacy of FluMist® (frozen formulation) against culture-confirmed influenza over 2 successive seasons, 1996-1997 and 1997-1998 (*Belshe 1998 & 2000a*). The primary endpoint of the trial was the prevention of culture-confirmed influenza illness. A total of 1602 children aged 15 to 71 months were randomized 2:1 (vaccine: placebo) during the first year of the study. The surveillance period for efficacy began 15 days after the first dose of vaccine or placebo and continued throughout the influenza season (approximately 6 months).

AV006 Year 1: In the first year of AV006 (1996-1997 season), both type A (H3N2) and type B strains circulated (*Belshe 1998*). As shown in Table 10, when compared with placebo recipients, FluMist® recipients experienced a significant reduction in the incidence of 1) culture-confirmed influenza (efficacy 93%, 95% CI: 87, 96), 2) culture-confirmed influenza associated with fever (efficacy 95%, 95% CI: 90, 98), and 3) culture-confirmed influenza associated with acute otitis media (efficacy 98%, 95% CI: 86, 100). The efficacy against culture-confirmed influenza associated with lower respiratory illness was not significantly different from placebo in year 1 (efficacy 83%, 95% CI: -15, 98).

- In the subset of children who received a single dose of FluMist® (n=189) or placebo (n=99), FluMist® was associated with 89% efficacy (95% CI: 65, 96) against culture-confirmed influenza (any strain), 87% efficacy (95% CI: 47, 96) against type A (H3N2), and 91% efficacy (95% CI: 46, 99) against type B strains (*Belshe 1998*). See Figure 10A.

- In the subset of children who were initially seronegative (i.e., baseline serum antibody levels ≤1:4 to the strains in the vaccine) and studied for hemagglutination-inhibiting antibody changes (n=203), HAI titers increased by 4-fold in 61% to 96% of vaccinees after 2 doses, depending on the influenza strain. A full response (defined as >4-fold increase) occurred in 88% to 92% of vaccinees after 1 dose for the B and A/H3N2 strains, but only 16% of vaccinees for A/H1N1 strain. See Table 11A for details.

Table 10.— Studies AV006 and AV011: Efficacy of FluMist® in Children (Aged 15 to 91 Months)

Endpoint	Incidence n(%)		Vaccine Efficacy	(95 % CI)
	FluMist®	Placebo		
AV006 Year 1	**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, 97.6)
AV006 Year 2	**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)
AV011	**n=144**	**n=78**		
Type A/H1N1 Vaccine Virus Shedding	6 (4.2)	19 (24.7)	82.9	(60.2, 92.7)

- Approximately one third of the study children were vaccinated in August/September (406 FluMist®, 204 placebo). Their season-long FluMist® efficacy rate versus placebo was 91.9% ($p < 0.001$). Overall, this post-hoc analysis showed there was no significant difference in efficacy rate with respect to month of administration in this study. See Table 11B.

Table 11A.— Study AV006: HAI Responses After 1 or 2 Doses of LAIV (FluMist®) or Placebo[a]

Study Group and Virus Type	Number Tested	Number Seronegative Before Vaccination[b]	Number of Seronegative Children With Antibody Response[c]		
			Day of Dose 1 to Before Dose 2[d]	Day of Dose 2 to 28 Days Afterward[e]	Day of Dose 1 to 28 Days After Dose 2
			Number/Total Number Tested (%)		
FluMist®					
A(H1N1)	136	89	14/86 (16)	33/60 (55)	45/74 (61)
A(H3N2)	136	66	59/64 (92)	3/4 (75)	54/56 (96)
B	136	93	80/91 (88)	6/8 (75)	75/78 (96)
Placebo					
A(H1N1)	67	47	0/45	1/38 (3)	1/40 (2)
A(H3N2)	67	30	1/27 (4)	2/23 (9)	3/27 (11)
B	67	42	0/39	1/35 (3)	1/38 (3)

[a] Adapted from Belshe et al. 1998.
[b] A seronegative result was defined as an antibody titer of 1:4 or less.
[c] An antibody response was defined as an increase in the antibody titer by a factor of 4 or more.
[d] Post-vaccination serum was drawn before the second dose of vaccine or on day 35 to day 49 among children in the 1-dose cohort.
[e] This group included subjects who were seronegative (titer ≤1:4) after the first dose and who had serum samples available for testing after the second dose.

Table 11B.— Study AV006: FluMist® Efficacy by Month of First Vaccination (Year 1 Data)

		Group	Cases of Influenza	Total No. Vaccinees	Efficacy (F vs. P)	Confidence Interval[a]	*p*-Value (F vs. P)	*p*-Value[b] (Oct/Nov vs. Aug/Sept)
All children 15-72 months of age	Oct/ Nov	FluMist®	4	443	94.8%	(86.3, 98.1)	<0.001	0.733 (no difference)
		Placebo	36	206				
	Aug/ Sept	FluMist®	6	404	91.9%	(81.5, 96.4)	<0.001	
		Placebo	37	206				

[a] Koopman's method.
[b] Breslow and Day's test for homogeneity of odds ratios for stratified tables.

AV006 Year 2: A total of 1358 of the original 1602 children (85%) returned for the second year of AV006 (1997-1998 season) (*Belshe 2000a*). The children remained in the same treatment group as in year 1 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 AV006, the epidemic H3N2 strain, A/Sydney/05/97, differed antigenically from the H3N2 strain included in the vaccine, A/Wuhan/359/95. Despite the appearance of this unexpected "drifted" strain resulting in a vaccine mismatch, the FluMist® group demonstrated similar efficacy as in year 1 for culture-confirmed influenza (87%, 95% CI: 78, 93), culture-confirmed influenza associated with fever (89%, 95% CI: 80, 94), and culture-confirmed influenza associated with otitis media (94%, 95% CI: 78, 99).

- After revaccination, 82%, 100%, and 100% of subjects in the FluMist® group had antibody (HAI titer >1:8) to H1N1, H3N2, and B strains, respectively. In contrast, only 20%, 65%, and 46% of placebo recipients had HAI antibody to vaccine antigens, respectively. See Figure 10B.

- In addition to the HAI antibody to the strain of H3N2 contained in the FluMist® vaccine (A/Wuhan/359/95), the H3N2 antibodies cross-reacted with the variant drift strain (A/Sydney/5/97). These cross-reactive antibodies (heterotypic immunity) were present in 98% of FluMist® subjects compared with only 60% of placebo recipients.

- In year 2, lower respiratory tract disease was present at the time of culture-confirmed influenza in 8 placebo recipients and in none of the vaccinated children (vaccine efficacy = 100%, CI = 77-100).

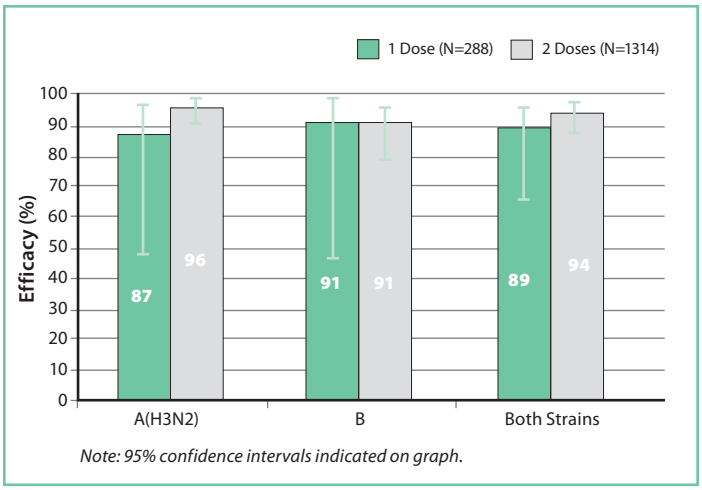

Figure 10A.—Prelicensure efficacy of FluMist® in children: 1 dose versus 2 doses (1996-1997). FluMist® demonstrated similar efficacy for 1- and 2-dose regimens. (Reprinted from *N Eng J Med*,1998;338:1405-1412, Belshe et al.)

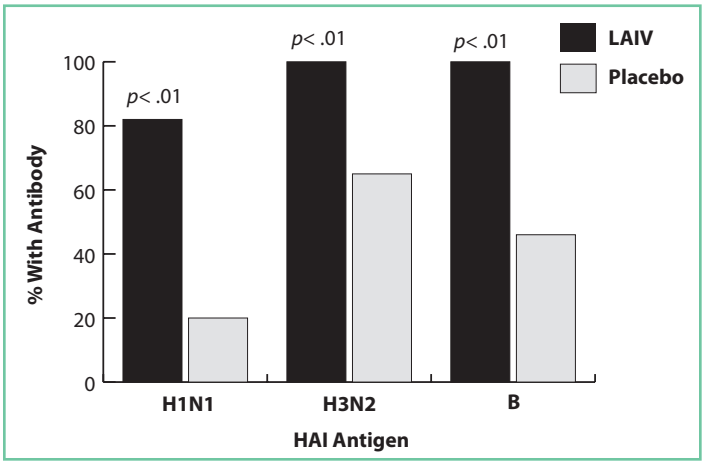

Figure 10B.—Study AV006: HAI responses after 1 dose of FluMist® or placebo in second year of vaccination. (Reprinted from *J Pediatr*, Vol 136, Belshe et al., Efficacy of vaccination with live attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine against a variant [A/Sydney] not contained in the vaccine, page 172, ©2000, with permission from Elsevier.)

Overall, in Study MI-CP111, FluMist® showed a 54.9% reduction in culture-confirmed influenza illness relative to TIV ("flu shot").

—Belshe 2007

Study AV011—Subset Challenge Trial

Because wild-type A (H1N1) did not circulate in the United States during either year of AV006, a separate study (AV011) was carried out (April to June, 1998) to estimate the protective efficacy of FluMist® against a simulated challenge with the H1N1 vaccine strain (*Belshe 2000b*) (see Table 10). The study was a multicenter, randomized, double-blind, open-label challenge study conducted in a subset of 222 children (now aged 34 to 91 months) who had received FluMist® (n=144) or placebo (n=78) for the past 2 years in the AV006 study. The primary efficacy endpoint of the study was shedding of H1N1 virus in respiratory secretions on days 1 to 4 after the vaccine virus challenge (the strain used for the challenge was A/Shenzhen 227/95-like H1N1). Hypothetically, those protected by the FluMist® vaccine—which was administered 6 to 8 months earlier—should have less shedding than placebo recipients when challenged with the H1N1 vaccine virus. The results showed 6 of 144 FluMist® recipients and 19 of 78 placebo recipients shed H1N1 virus on 1 or more days after challenge. The efficacy of FluMist® against this H1N1 challenge was 83% (95% CI: 60, 93). Furthermore, previously vaccinated children terminated viral shedding (within 3 days) significantly sooner than did previous placebo recipients (p=0.0001).

Please see accompanying Full Prescribing Information (Package Insert).

Study MI-CP111— Comparative Safety and Efficacy

MI-CP111 was a pivotal, Phase 3 study designed to evaluate the efficacy and safety of FluMist® (refrigerated formulation) compared with TIV ("flu shot") in children less than 5 years of age (*Belshe 2007*). It was a randomized, double-blind, multinational study that enrolled 8475 children who were 6 to 59 months of age.

The primary efficacy endpoint was the relative efficacy of FluMist® versus TIV against culture-confirmed modified CDC-ILI (see footnote) caused by wild-type strains antigenically similar to those contained in the vaccine. The study was conducted during the 2004-2005 influenza season in 16 countries in North America, Europe, the Middle East, and Asia. Subjects were randomized at a 1:1 ratio to receive either intranasal FluMist® plus intramuscular placebo (N=4243), or intramuscular TIV plus intranasal placebo (N=4232). Randomization was stratified by age at first dose (6-23, 24-35, or 36-59 months of age), prior influenza vaccination status, a history of 3 or more wheezing illnesses requiring medical follow-up or hospitalization, and country.

A secondary study endpoint was incidence of culture-confirmed modified CDC-ILI occurring at least 14 days after last vaccination and caused by antigenically dissimilar strains (aka "drift strains" or "mismatched strains"). Note: the dominant influenza virus strain (51% of all isolates) during the 2004-2005 season was Type A/H3N2, and 78% of all H3N2 strains antigenically characterized by the CDC in the United States that season were antigenically drifted from the vaccine strain (see Table 3 and CDC Web page: http://www.cdc.gov/flu/weekly/fluactivity.htm).

The efficacy results of MI-CP111 are shown in Tables 12 & 13 and Figure 11. These data are for the entire study population. (Note: FluMist® is indicated for children ≥ 2 years of age.) FluMist® demonstrated statistically superior efficacy compared with TIV against culture-confirmed modified CDC-ILI due to matched strains, with a relative efficacy of 44.5% (95% CI: 22, 61). FluMist® was also highly efficacious compared with TIV against culture-confirmed modified CDC-ILI due to mismatched ("antigenically dissimilar") strains, with a relative efficacy of 58.2% (95% CI: 47, 67). As shown in Table 12, most of the mismatched ("antigenically dissimilar") strains were Type A/H3N2. Overall, FluMist® showed a 54.9% (95% CI: 45, 63) reduction in influenza illness relative to TIV for modified CDC-ILI due to any influenza strain regardless of antigenic match. FluMist® had significantly greater efficacy against influenza A viruses, both well-matched to those in the vaccine (89% fewer cases of influenza illness caused by matched H1N1 viruses) as well as those mismatched to the vaccine virus (79% fewer cases of influenza illness caused by mismatched H3N2 viruses). FluMist® recipients had 27% fewer cases of influenza illness caused by matched influenza B strains compared with TIV recipients; this difference did not reach statistical significance. No difference was seen for B strains not well matched to the vaccines.

Significant reductions also were seen in the overall attack rates of acute otitis media and lower respiratory illnesses associated with positive influenza cultures, with a relative efficacy for the FluMist® group of 50.6% (p=0.04) and 45.9% (p=0.046), respectively (*Belshe 2007*).

FOOTNOTE—CDC-ILI (CDC-defined influenza-like illness), defined as fever (temperature >100˚F oral or equivalent) plus cough or sore throat on the same or consecutive days, was modified ("modified CDC-ILI") to fever plus cough, sore throat, or runny nose/nasal congestion as a means of capturing age-appropriate influenza illness symptoms per discussions with the FDA Center for Biologics Evaluation and Research (CBER). Culture-confirmed modified CDC-ILI was defined as a positive culture for a wild-type influenza virus associated within ±7 days of modified CDC-ILI symptoms.

Table 12.— Study MI-CP111: Relative Efficacy Against Culture-Confirmed Modified CDC-ILI Caused by Wild-Type Strains

	LAIV (refrigerated FluMist®)			TIV			Relative Efficacy*	95% Exact CI for Relative Efficacy*
	N	# of Cases	Crude Attack Rate (cases/N)	N	# of Cases	Crude Attack Rate (cases/N)		
Antigenically Similar (Vaccine Match)								
All strains	3916	53	1.4%	3936	93	2.4%	**44.5%**	22.4, 60.6
A/H1N1	3916	3	0.1%	3936	27	0.7%	**89.2%**	67.7, 97.4
A/H3N2	3916	0	0.0%	3936	0	0.0%	—	—
B	3916	50	1.3%	3936	67	1.7%	**27.3%**	-4.8, 49.9
All strains, ITT	4243	55	1.3%	4232	100	2.4%	**46.0%**	25.2, 61.4
Antigenically Dissimilar (Vaccine Mismatch)								
All strains	3916	102	2.6%	3936	245	6.2%	**58.2%**	47.4, 67.0
A/H1N1	3916	0	0.0%	3936	0	0.0%	—	—
A/H3N2	3916	37	0.9%	3936	178	4.5%	**79.2%**	70.6, 85.7
B	3916	66	1.7%	3936	71	1.8%	**6.3%**	-31.6, 33.3
Regardless of Antigenic Match								
All strains	3916	153	3.9%	3936	338	8.6%	**54.9%**	45.4, 62.9
A/H1N1	3916	3	0.1%	3936	27	0.7%	**89.2%**	67.7, 97.4
A/H3N2	3916	37	0.9%	3936	178	4.5%	**79.2%**	70.6, 85.7
B	3916	115	2.9%	3936	136	3.5%	**16.1%**	-7.7, 34.7

According-to-Protocol (ATP) population, except where noted as Intention-to-Treat (ITT).

*Relative efficacy was adjusted for country, age, prior vaccination status, and recurrent wheezing history status.

Table 13.— Study MI-CP111: Efficacy by Age Against Matched Strains*

Age Group (months)	LAIV (refrigerated FluMist®)			TIV			Relative Efficacy*	95% Exact CI for Relative Efficacy*
	N	# of Cases	Crude Attack Rate (cases/N)	N	# of Cases	Crude Attack Rate (cases/N)		
6-23	1834	23	1.3%	1852	32	1.7%	**29.1%**	-21.2, 59.1
24-59	2082	30	1.4%	2084	61	2.9%	**52.5%**	26.7, 69.7

*Relative efficacy was adjusted for country, age, prior vaccination status, and recurrent wheezing history status.

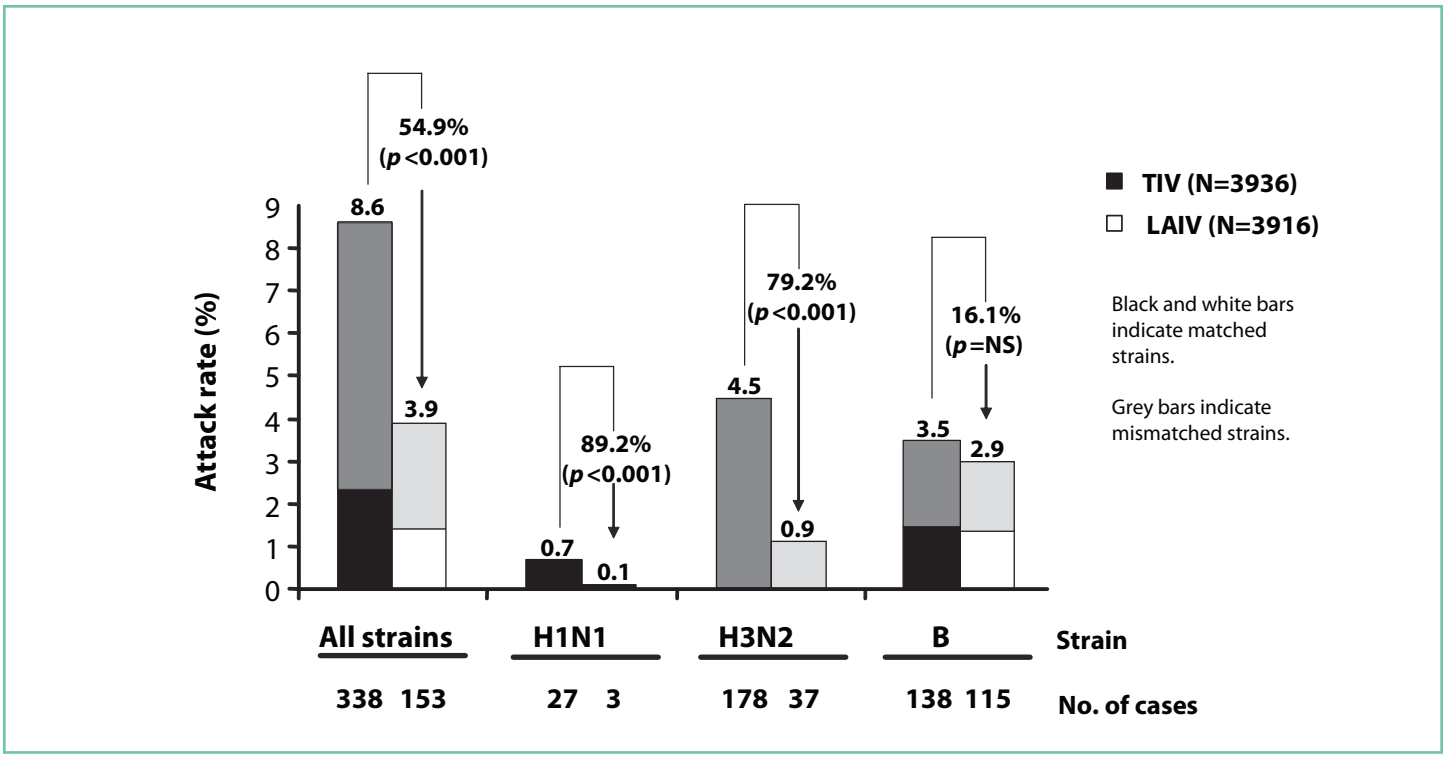

Figure 11.—MI-CP111: relative efficacy against culture-confirmed modified CDC-ILI caused by wild-type strains (according to protocol population).

Study D153-P501—Pan-Asian 2-Year Pediatric Efficacy

Study D153-P501 was a randomized, double-blind, placebo-controlled efficacy, safety, and immunogenicity (subset) study of FluMist® in healthy children 12 to 35 months of age, conducted at multiple sites in Asia during the 2000-2001 and 2001-2002 seasons (*Tam 2007*). A total of 3174 subjects were randomized in year 1 of the study to receive 2 doses of FluMist® 28 to 56 days apart, followed by re-randomization and administration of a single dose of FluMist® or placebo in year 2 of the study.

Findings showed that FluMist® in year 1 had a relative efficacy of 73% vs. placebo. (See Table 14.) In the subsequent season (year 2), if only placebo was re-administered, the relative efficacy was 56% (indicating a carryover benefit from the previous season). When FluMist® was given in the second year, relative efficacy (versus placebo) was 84%, which demonstrates the value of annual revaccination.

The durability of vaccine protection was also assessed with regard to variation in seasonal onset and duration of local influenza epidemic activity. In 2 countries (Malaysia and Philippines) that experienced late

Table 14.—Study D153-501: Efficacy of CAIV-T Against Influenza Illness Due to Subtypes Antigenically Similar to Vaccine (*adapted from Tam 2007*)

Children dosed with		Children dosed with	Relative efficacy (95% CI)	In year
CAIV-T, Year 1	vs.	Placebo, Year 1	73% (63,81)	1
CAIV-T, Year 1 Placebo, Year 2	vs.	Placebo, Year 1 Placebo, Year 2	56% (31,73)	2
CAIV-T, Year 1 CAIV-T, Year 2	vs.	Placebo, Year 1 Placebo, Year 2	84% (70,92)	2

Efficacy at 1 to <5 months post-vaccination was comparable to that at 9 to 12 months for A/H1N1 and A/H3N2 strains and at 5 to 7 months for B strains. Meaningful efficacy was seen through a second season without vaccination, although at a lower level than during the first 12 months post-vaccination.

—Ambrose 2008

influenza outbreaks (began 5.5 to 9 months after the second dose and continued through 10.5 to 13 months after the second dose), vaccine efficacy was 72.9% (95% CI: 51.5, 85.5) against antigenically similar A/H1N1, A/H3N2, and B. This efficacy was comparable to the efficacy seen in the overall study in year 1 against antigenically similar strains (73%, 95% CI: 63, 81).

Subgroup Analyses in Children 2 to 7 Years of Age

A subgroup analyses of these 3 pivotal pediatric trials showed FluMist® reduced the incidence of culture-confirmed ILI in subjects 2 to 7 years of age by 69 to 95% compared with placebo and in subjects 2 to 5 years of age by 54% compared with TIV ("flu shot"). When assessed across all endpoints, efficacy was observed during seasons in which antigenically matched and mismatched strains circulated and when influenza circulated 5.5 to 13 months after vaccination (*Belshe 2008*).

Effectiveness in Children

In addition to evaluating culture-confirmed efficacy, AV006 also measured the effectiveness of FluMist® in reducing 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. Statistically significant reductions in febrile illnesses and febrile otitis media with antibiotic use (regardless of influenza culture results) were seen in year 1 and in missed day care/school, parental lost work days, and health care provider visits (for children with influenza-positive cultures) in year 1 and/or year 2. For details, please see Table 15.

Table 15.—Effectiveness of FluMist® in Children (Study AV006)

Endpoint	Rate per Participant		Percent Reduction	*p* Value[a]
Trial 1 Year 1	**FluMist®**	**Placebo**		
Febrile Illness With Antibiotics[b]	0.31	0.46	**31.0**	<0.01[d]
Febrile Otitis Media With Antibiotics[b]	0.14	0.22	**35.0**	<0.01[d]
Missed Day Care/Preschool/School				
All Illness[b]	0.76	0.84	**9.4**	0.34
Culture-Positive Illness	0.01	0.17	**94.4**	<0.01[d]
Parental Lost Work Days				
All Illness[b]	0.26	0.31	**16.8**	0.24
Culture-Positive Illness	0.00[c]	0.08	**97.7**	<0.01[d]
Health Care Provider Visits				
All Illness[b]	1.20	1.39	**13.4**	0.02[d]
Culture-Positive Illness	0.01	0.14	**93.9**	<0.01[d]
Trial 1 Year 2				
Febrile Illness With Antibiotics[b]	0.30	0.34	**10.6**	0.18
Febrile Otitis Media With Antibiotics[b]	0.11	0.13	**20.9**	0.04[d]
Missed Day Care/Preschool/School				
All Illness[b]	0.93	1.11	**16.6**	0.01[d]
Culture-Positive Illness	0.02	0.23	**92.5**	<0.01[d]
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[d]
Health Care Provider Visits				
All Illness[b]	0.95	1.02	**7.0**	0.18
Culture-Positive Illness	0.01	0.09	**88.9**	<0.01[d]

[a]Unadjusted for multiple comparisons, Wilcoxon Rank Sum test.
[b]For all participants with illness events regardless of whether a culture was obtained.
[c]Exact value is 0.0019.
[d]Indicates statistically significant difference vs. placebo.

Efficacy in Adults

AV003 was a multicenter, randomized, double-blind, placebo-controlled challenge trial performed in 92 healthy adults 18 to 40 years of age who were seronsusceptible to at least 1 strain included in the vaccine (*Treanor 2000*). The primary endpoint of the study was to compare the efficacy of FluMist® and a US-licensed injectable trivalent inactivated influenza vaccine (TIV) against laboratory-documented (culture or serology) influenza illness after challenge with wild-type influenza viruses. (Note—a challenge study is limited by the exposure conditions and virus strains used in the trial.) Adults were randomized to receive either FluMist® (n=29), inactivated influenza virus vaccine (n=32), or placebo (n=31). After subsequent intranasal administration of the wild-type challenge viruses, the overall efficacy rates of FluMist® and inactivated influenza vaccine against laboratory-documented influenza illness were 85% and 71%, respectively, compared with placebo. These efficacy rates were statistically similar. For details, please see Table 16.

Table 16.— Efficacy of FluMist® in Adults in a Challenge Study (Study AV003)

Incidence (n) and Efficacy Against Laboratory-Documented Influenza After Wild-Type Challenge				
Group	**N**	**n (%)**	**Efficacy[a]**	**95% CI**
FluMist®	29	2 (7)	**85**	(28, 100)
TIV[b]	32	4 (13)	**71**	(2, 97)
Placebo	31	14 (45)	—	

[a] Comparisons are statistically significant versus placebo, but there was no significant difference when comparing TIV versus FluMist®.
[b] Trivalent inactivated virus vaccine ("flu shot").

Effectiveness in Adults

The Adult Effectiveness Study (AV009) was a multi-center, randomized, double-blind, placebo-controlled trial designed to evaluate the effectiveness of FluMist® in reducing 1) illness, 2) illness-associated days of absenteeism from work, and 3) days of health care utilization during influenza outbreaks (*Nichol 1999*). A total of 4561 healthy adults 18 to 64 years of age (2489 women and 2072 men) were randomized 2:1 (vaccine:placebo) and vaccinated during the 1997-1998 season (concurrent to the second year of the AV006 Pediatric Efficacy Study). 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). Cultures for influenza virus from individual subjects were not obtained. Symptoms were measured via individual reports using structured reporting diaries. Adults were characterized as having AFI if they had symptoms for at least 2 consecutive days with fever on at least 1 day and if they had 2 or more symptoms (fever, chills, headache, runny nose, sore throat, cough, muscle aches, tiredness/weakness) on at least 1 day. SFI was defined as at least 3 consecutive days of symptoms (fever, chills, headache, runny nose, sore throat, cough, muscle aches, tiredness/weakness), at least 1 day of fever, and 2 or more symptoms on at least 3 days. FURI was defined as at least 2 consecutive days of upper respiratory symptoms (runny nose, sore throat, or cough), fever on at least 1 day, and 2 symptoms on at least 1 day.

Please see accompanying Full Prescribing Information (Package Insert).

As shown in Table 17, there were significant reductions for the incidence of SFI and FURI (but not AFI) in FluMist® subjects compared with placebo recipients. FluMist® recipients exhibited a 23% reduction in days of illness with AFI, a 27% reduction in days of illness with SFI, and a 25% reduction in days of illness with FURI compared with placebo. Days of prescription antibiotic use were significantly decreased across all 3 febrile illness definitions. Days of health care provider visits and illness-associated days of missed work were both statistically significantly decreased for SFI and FURI.

As in the AV006 Pediatric Efficacy Study (*Belshe 2000a*), these findings were seen during a season (1997-1998) in which the predominant circulating strain of influenza virus during the trial was A/Sydney/05/97 (H3N2), a "drift" strain that differed antigenically from the A/Wuhan (H3N2) strain contained in FluMist® (*Nichol 1999*). In studies conducted with inactivated influenza vaccine ("flu shot") in 1997-1998, no efficacy or effectiveness was seen (*Belshe 2000a*). Although the LAIV (FluMist®) and inactivated vaccines were not compared directly in this epidemic year, both the findings of AV006 and AV009 suggest that LAIV is more effective against viruses that are poorly matched to vaccine strains (*Belshe 2000a*).

Table 17.— Effectiveness of FluMist® in Healthy Adults[a] (Study AV009)

Endpoint	Incidence per Participant n (%)		Percent Reduction	95% CI
	FluMist® n=2833	Placebo n=1420		
Proportion With				
Any Febrile Illness (AFI)	373 (13.2)	207 (14.6)	**9.7**	(-5.8, 22.8)
Severe Febrile Illness (SFI)	285 (10.1)	173 (12.2)	**17.4**	(1.3, 30.8)
Febrile Upper Respiratory Illness (FURI)	240 (8.5)	154 (10.8)	**21.9**	(5.3, 35.5)
	Rate[b]			
	FluMist® n=2833	Placebo n=1420		
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)
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)
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)
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)

[a] Adapted from Nichol et al. 1999.
[b] Number of days per 1000 participants per 7-week site-specific outbreak period.

Product Bridging/ Comparative Immunogenicity Trial

Study MI-CP112 compared the immunogenicity, safety, and tolerability of frozen and refrigerated formulations of FluMist® in healthy individuals 5 to 49 years of age. There were 981 subjects randomized (1:1) to receive each formulation (*Block 2007*). Subjects 5 to 8 years of age (mean=6.5 years) received 2 doses of vaccine (46 to 60 days apart), while subjects 9 to 49 years of age (mean=26 years) received 1 dose of vaccine. Equivalent immunogenicity was defined as a serum hemagglutinin inhibition (HAI) geometric mean titer (GMT) ratio ≤2-fold for each of the 3 vaccine-specific strains. Reactogenicity and adverse events (AEs) were monitored through 28 days after the final dose.

Results were reported for 376 subjects 5 to 8 years old, and 566 subjects 9 to 49 years of age, who were eligible for analysis. Frozen and refrigerated FluMist® demonstrated equivalent post-vaccination HAI responses. (See Figure 12.) The GMT ratios of CAIV-T frig/FluMist® frozen (adjusted for baseline status) for the H1N1, H3N2, and B strains, respectively, were 1.24, 1.02, and 1.00 in the 5 to 8 years group and 1.14, 1.12, and 0.96 in the 9 to 49 years group (all results were within their 95% confidence intervals). Seroresponse rates (≥4-fold rise) were similar in both age groups for each of the 3 vaccine strains. The most frequent reactogenic event in both groups was runny nose/nasal congestion, which occurred at a higher rate after dose 1 compared with dose 2 for both refrigerated formulation (44% vs. 40%) and frozen FluMist® (42% vs. 29%). The incidence of any reactogenic events for refrigerated and frozen FluMist® were 69% and 57%, and 60% and 44%, for the 5 to 8 years and 9 to 49 years groups, respectively. AEs were similar between treatment groups and age cohorts, with no serious AEs related to study vaccine.

This study was the basis for FDA approval of the new refrigerated formulation commencing with the 2007-2008 season.

Please see accompanying Full Prescribing Information (Package Insert).

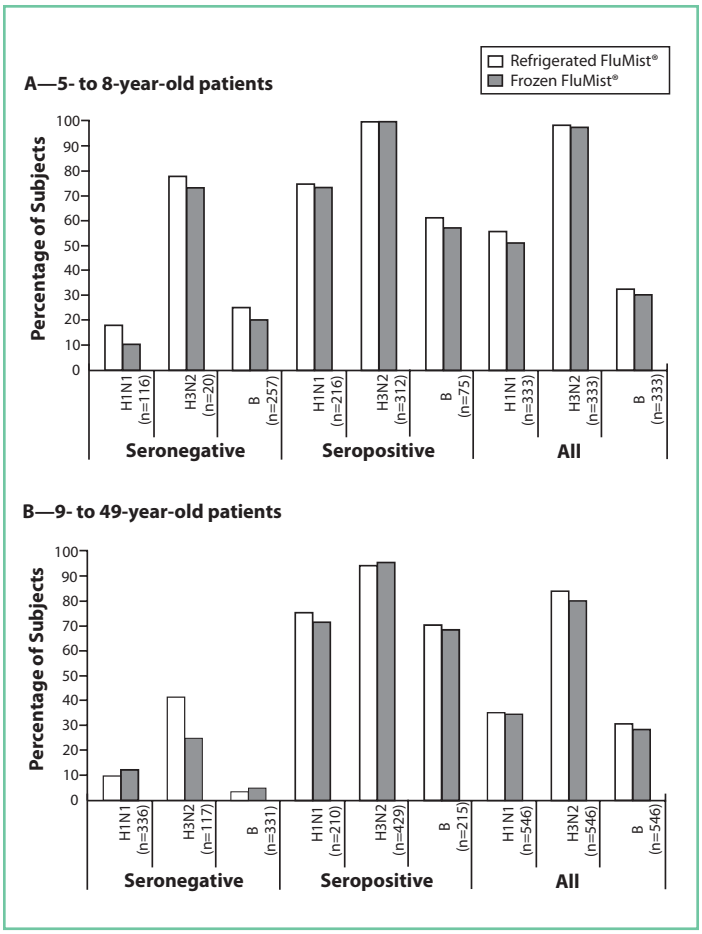

Figure 12.— MI-CP112: Proportion of subjects with post-vaccination HAI titer ≥1:32

Limits of the FluMist® Clinical Development Trials

Clinical development trials for FluMist® enrolled primarily healthy children and adults and excluded pregnant women or persons with chronic medical conditions involving, but not limited to, the cardiovascular and pulmonary systems. Such conditions include patients who required regular medical follow-up or hospitalization within the preceding 12 months because of chronic metabolic diseases (including diabetes), renal dysfunction, immunosuppression, or hemoglobinopathies. Because of these exclusions, there are limited available data and recommendations in the package insert (Full Prescribing Information) on the use of FluMist® in "high-risk conditions" (as categorized in CDC/ACIP 2008). Likewise, there is limited efficacy data in adults older than 49 years of age because of low enrollment of older patients. Nonetheless, data continue to be collected for FluMist® use in the elderly population (*de Villiers 2003*).

IV. Clinical Safety and Tolerability

The safety and tolerability of FluMist® (frozen and refrigerated formulations) were actively solicited or monitored in the clinical development trials. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. The most common adverse reactions (≥10% in FluMist® and at least 5% greater than in control) were runny nose or nasal congestion in all ages, fever >100°F in children 2-6 years of age, and sore throat in adults (per FluMist® package insert; see also Tables 18 and 19). Overall, the incidence of selected adverse reactions that may be complications of wild-type influenza (such as pneumonia, bronchitis, bronchiolitis, or central nervous system events) was observed to be similar in FluMist® and placebo groups.

Comprehensive safety data pooled mainly from pivotal clinical trials (Studies D153-P501, AV006, D153-P526, AV019, AV009, and MI-CP111) are described in the package insert. **See the FluMist® package insert (under heading "Adverse Reactions") for data specific to the 2-year-old to 49-year-old age group (i.e., the indicated age population).**

Safety and Tolerability Study Endpoints

FluMist® clinical trials collected data on up to 4 types of safety endpoints (described below). Additional studies for certain potential adverse events, such as asthma/wheezing, were also performed.

Reactogenicity

Reactogenicity events were specific signs and symptoms that would be possibly expected from vaccination and were recorded in each subject's diary card. The solicited reactogenicity events included runny nose/nasal congestion, sore throat, cough, irritability, headache, chills, vomiting, muscle aches, and decreased activity or a feeling of tiredness/weakness. Daily body temperature was also recorded. In general, these data were captured systematically for 7 days in adults after vaccination and for 10 days in children after each vaccine dose.

Other Adverse Events

Other adverse events were untoward events experienced after vaccination that were not otherwise defined as reactogenicity events. These events were recorded regardless of whether the event was judged related to vaccination.

Serious Adverse Events/ Medically Attended Events

Any event that was fatal or life-threatening, permanently disabling, required hospitalization or prolonged an existing hospitalization, a cancer, an overdose, or a congenital anomaly was considered a serious adverse event (SAE). Depending on the study, SAEs were collected for 28 days after dose administration in adults and for 42 days in children. In some recent studies, such as CP-111, SAEs that occurred any time during the study surveillance period (i.e., up to 180 days after a patient's last dose) were recorded.

Adverse Events in Placebo- and Active-Controlled Clinical Trials

A total of 9537 children and adolescents 1-17 years of age and 3041 adults 18-64 years of age received FluMist® in randomized, placebo-controlled trials (Studies D153-P501, AV006, D153-P526, AV019, and AV009). In addition, 4179 children 6-59 months of age received FluMist® in Study MI-CP111, a randomized, active-controlled trial. These are the primary studies from which adverse events were analyzed and reported in the package insert.

Details on these and other related data are provided below.

Children

Solicited Adverse Events (Reactogenicity) in Children

Table 18 shows an analysis of solicited reactogenic events reported in the package insert (from 3 pivotal trials) for children 2 to 6 years old. The largest absolute difference between FluMist® and placebo after dose 1 was an increase in runny nose/nasal congestion. Event rates were similar or less frequent in vaccinated children and placebo recipients after dose 2. Overall, events were transient, peaking on day 2 post-vaccination and generally lasting for 3 days or less.

Table 18.— Summary of Solicited Events Observed Within 10 Days After Dose 1 for Vaccine[a] and Either Placebo or Active Control Recipients; Children 2 to 6 Years of Age

	Studies D153-P501 and AV006		Study MI-CP111	
	FluMist® N=876-1764[c]	Placebo Spray N=424-1036[c]	FluMist® N=2170[c]	Active Control Injection[b] N=2165[c]
Event	**%**	**%**	**%**	**%**
Runny Nose/Nasal Congestion	58	50	51	42
Decreased Appetite	21	17	13	12
Irritability	21	19	12	11
Decreased Activity (Lethargy)	14	11	7	6
Sore Throat	11	9	5	6
Headache	9	7	3	3
Muscle Aches	6	3	2	2
Chills	4	3	2	2
Fever				
100-101˚F Oral	9	6	6	4
101-102˚F Oral	4	3	4	3

[a]Frozen formulation used in AV006; refrigerated formulation used in D153-P501 and MI-CP111.
[b]TIV-Injectable influenza vaccine.
[c]Number of evaluable subjects (those who returned diary cards) for each event. Range reflects differences in data collection between the 2 pooled studies.

Please see accompanying Full Prescribing Information (Package Insert).

In children less than 5 years of age, there was no significant difference in the rates of solicited adverse events between the FluMist® and placebo groups (see Table 19).

Long-term Use/Annual Vaccination

After revaccination in year 2 of the Pediatric Efficacy Study (AV006), there were no significant differences between FluMist® and placebo for rhinorrhea, fever, or decreased activity (*Belshe 2000a*). The study then continued as an open-label phase 3 safety trial (AV015 & AV017) and eventually reported safety outcomes for 4 consecutive seasons (*Piedra 2002a*). See Table 20.

In the subset of 641 children who received FluMist® across 3 consecutive years, the proportion reporting "any symptom" or any specific reactogenicity event was similar or less in the second and third years (*Piedra 2002a*). The largest rate difference between the second and third years was in runny nose/nasal congestion (42% versus 37%, respectively). For the subset of 545 children who received FluMist® across 4 consecutive years, there was a further decline in "any symptoms," and all other individual symptoms were similar or slightly lower. Please see Table 20 for details.

Other Adverse Events in Children

In addition to the solicited events, "other" adverse events (non-reactogenicity) were collected during investigator monitoring of the clinical trials. In the data analysis of children 1 to 8 years of age

Table 19.— Summary of Solicited Events Observed Within 10 Days After Dose 1 for FluMist® Recipients <60 and ≥60 Months of Age From Pivotal Studies AV006 and AV019 (data on file).

	<60 Months of Age				5-17 Years of Age			
	FluMist®		Placebo		FluMist®		Placebo	
Number Vaccinated	1299		560		234		101	
Number Returning Diary Cards[a]	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)
Runny Nose/Nasal Congestion	778/1241	(62.7)	263/535	(49.2)	103/214	(48.1)	42/ 95	(44.2)
Irritability	387/1286	(30.1)	159/558	(28.5)	45/231	(19.5)	17/101	(16.8)
Cough	341/1286	(26.5)	154/558	(27.6)	62/231	(26.8)	33/101	(32.7)
Decreased Activity	208/1241	(16.8)	72/535	(13.5)	30/214	(14.0)	12/ 95	(12.6)
Sore Throat	102/1286	(7.9)	33/558	(5.9)	29/231	(12.6)	20/101	(19.8)
Vomiting	89/1241	(7.2)	25/535	(4.7)	10/214	(4.7)	3/ 95	(3.2)
Headache	81/1241	(6.5)	25/535	(4.7)	38/214	(17.8)	11/ 95	(11.6)
Muscle Aches	66/1241	(5.3)	16/535	(3.0)	13/214	(6.1)	4/ 95	(4.2)
Chills	54/1241	(4.4)	21/535	(3.9)	13/214	(6.1)	5/ 95	(5.3)
Fever[b]								
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]The diary cards used in the various clinical trials did not contain all of the same solicited adverse event terms, thus the denominators in the event rates are not always the same.

[b]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.

(pivotal trial AV006, data on file), these events that occurred in 1% or more of FluMist® recipients and at a higher rate in FluMist® recipients compared with children receiving placebo were abdominal pain, otitis media, accidental injury, diarrhea, rhinitis, anorexia, infection, and rash. Subsequent trials cited in the current package insert under ADVERSE REACTIONS report "other reactions" consistent with this early pivotal trial.

Serious/Medically Attended Events in Children and Adolescents Aged 1 to 17 Years

The largest randomized placebo-controlled trial (*study protocol AV019—Bergen 2004, Black 2002 & 2006*) in 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 9689 evaluable children 1 to 17 years of age, including 4762 males and 4927 females, were randomized 2:1 (vaccine:placebo). Of these 9689 children, there were 5638 who were 1 to 8 years of age and 4051 who were 9 to 17 years of age. For children younger than 9 years of age, dose 2 was administered 28 to 42 days after dose 1.

Table 20.— Sequential Annual Doses of FluMist®: Percentage of Recipients Who Experienced Symptoms Between Day 0 and Day 10 After Vaccination from Studies AV006, AV015, and AV017 (Pedra 2002a)[a]

Symptoms	Year 1 Dose 1 (N=1056)	Year 2 (N=912)	Year 3 (N=641)	Year 4 (N=545)
Any symptom	74%	58%	55%	50%
Runny nose or nasal congestion	59%	42%	37%	37%
Sore throat	10%	10%	8%	11%
Cough	28%	24%	27%	27%
Vomiting	6%	5%	5%	3%
Muscle ache	5%	3%	3%	4%
Headache	8%	9%	10%	11%
Chills	4%	3%	2%	2%
Decreased activity	16%	11%	10%	10%
Fever 1[b]	16%	11%	8%	7%
Fever 2[c]	7%	6%	3%	3%

[a]Reproduced with permission from Piedra PA, et al. *Pediatrics*, Vol. 110, Page(s) 662-672, Table 7, Copyright 2002.
[b]Oral >100.0˚F or rectal/aural >100.6˚F, or axillary/missing method >99.6˚F.
[c]Oral >101.0˚F or rectal/aural >101.6˚F, or axillary/missing method >100.6˚F.

Please see accompanying Full Prescribing Information (Package Insert).

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 4 pre-specified grouped diagnoses: acute respiratory tract events, systemic bacterial infections, acute gastrointestinal tract events, and rare events potentially related to influenza. For these 4 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 FluMist® was not associated with increased risk for these illnesses in any protocol-specified analysis. No systemic bacterial infection occurred. In FluMist® recipients, no increased risk was observed for rare events that have been reported with naturally occurring influenza virus infection, including seizure(s), febrile seizures, and epilepsy. No cases of encephalitis, acute idiopathic polyneuritis (Guillain-Barre syndrome), Reye syndrome, or myocarditis (all influenza-associated rare disorders) were reported in this study.

In this study (*Bergen 2004, Black 2002*), there were approximately 1500 MAE analyses. FluMist® was associated with a significantly increased risk in 14 individual MAE categories and with significantly decreased risk in 21 individual MAE categories. Of the 14 individual MAE categories for which FluMist® was associated with increased risk, a biological association with FluMist® was plausible for 6: upper respiratory infection (URI), musculoskeletal pain, asthma, abdominal pain, otitis media with effusion (OME), and adenitis/adenopathy. After additional analysis, a cause-and-effect relationship could not be excluded for FluMist® and URI. In addition, in children younger than 60 months of age, a cause-and-effect relationship could not be excluded for FluMist® and asthma events (discussed further in Special Populations). Of the 21 individual MAE categories for which FluMist® was associated with decreased risk, a biologically plausible association with FluMist® existed for 10: abdominal pain, acute gastroenteritis, conjunctivitis, cough, diarrhea, febrile illness, otitis media, pharyngitis, tonsillitis, and viral syndrome.

Adults

Solicited Adverse Events (Reactogenicity) in Adults

In the 5 placebo-controlled studies in healthy adults 18 to 64 years of age combined (AV001, AV003, AV004, AV009, and DMID98-005), the largest absolute differences observed between FluMist® and placebo recipients reporting any individual event following a single dose were in runny nose (43.6% FluMist® versus 27.0% placebo), sore throat (25.8% FluMist® versus 16.5% placebo), and tiredness/weakness (24.5% FluMist® versus 20.6% placebo). Incidence of fever greater than 100°F was similar in FluMist® and placebo recipients after a single dose (1.3% versus 1.5%, respectively). Please see Table 21A for details.

Table 21A.—Summary of Solicited Events Observed Within 7 Days After Each Dose for Vaccine and Placebo Recipients (Healthy Adults 18 to 64 Years of Age)

	FluMist® 3264	Placebo 1619
Event	**(%)**	**(%)**
Any Event	69.6	60.7
Cough	13.3	10.5
Runny Nose	43.6*	27.0
Sore Throat	25.8*	16.5
Headache	39.4	37.1
Chills	8.0	6.0
Muscle Aches	15.7	14.3
Tiredness/Weakness	24.5	20.6
Fever		
Temp >100˚F	1.3	1.5
Temp >102˚F	0.1	0.1
Temp >104˚F	0.0	0.0

*Denotes statistically significant *p*-value ≤0.05; no adjustments for multiple comparisons; Fisher's Exact Method.

For the subset of 641 children who received FluMist® across 3 consecutive years, the proportion reporting "any symptom" or any specific reactogenicity event was similar or less in the second and third years.

—Piedra 2002a

In studies, serious adverse events have occurred at a low rate (<1%) in FluMist® and placebo recipients in both children 1 to 17 years of age and adults 18 to 64 years of age. None were reported as related to vaccination.

In the subset of 4561 healthy adults 18 to 64 years of age in study AV009, runny nose and sore throat were reported significantly more often in FluMist® patients than in placebo patients (*Nichol 1999*). The incidence and profile of solicited reactogenicity events for the subset of adults aged 18 to 49 years differed from that of the entire 18- to 64-year-old cohort in that cough, chills, and tiredness/weakness also were reported more frequently in vacinees compared with placebo recipients ($p \leq 0.05$) in addition to runny nose and sore throat ($p \leq 0.05$). See Table 21B. Reactogenicity events in adults were transient and usually lasted 1 or 2 days. These events did not prompt increased use of over-the-counter medications or prescription antibiotics in vaccine recipients (*Nichol 1999*).

Table 21B.— Summary of Solicited Events Observed Within 7 Days After Each Dose for Vaccine and Placebo Recipients (Healthy Adults 18 to 49 Years of Age)

	FluMist N=2548[a]	Placebo N=1290[a]
Event	**(%)**	**(%)**
Any event	71.9[b]	62.6
Cough	13.9[b]	10.8
Runny Nose	44.5[b]	27.1
Sore Throat	27.8[b]	17.1
Headache	40.4	38.4
Chills	8.6[b]	6.0
Muscle Aches	16.7	14.6
Tiredness/Weakness	25.7[b]	21.6
Fever		
Oral Temp >100˚F	1.5	1.3
Oral Temp >101˚F	0.5	0.7
Oral Temp >102˚F	0.1	0.2
Oral Temp >103˚F	0.0	0.0

[a]Number of evaluable subjects (those who returned diary cards). [97.9% of FluMist® recipients and 97.9% of placebo recipients.]
[b]Denotes statistically significant *p*-value ≤ 0.05; no adjustments for multiple comparisons; Fisher's Exact Method.

Other Adverse Events in Adults

In addition to the solicited events, participants also reported "other" adverse events that occurred during the course of the clinical trials. Events occurring in at least 1% of FluMist® recipients and at a higher rate compared with placebo were nasal congestion (9% FluMist® vs. 2% placebo) and sinusitis (4% FluMist® vs. 2% placebo).

Serious Adverse Events (SAE)

In studies, serious adverse events have occurred at a low rate (<1%) in FluMist® and placebo recipients in both children 1 to 17 years of age and adults 18 to 64 years of age.

Serious adverse event data in children younger than 5 years of age from 13 clinical studies of FluMist® were analyzed through 42 days and through 180 days after vaccination (*VRBPAC, May 2007*). These studies included a combined total of >18,000 FluMist® recipients, >6600 placebo recipients, and >5000 TIV recipients. Integration across the placebo-controlled, TIV-controlled, and uncontrolled trials demonstrated a similar incidence of SAEs for FluMist®, TIV, and placebo recipients. Nearly all of the SAEs were hospitalizations, and the most common were gastro-intestinal and lower respiratory disorders. The relative frequencies of these and other SAEs of special interest, i.e., SAEs associated with reactogenicity events or with wheezing, were also similar for FluMist®, TIV, and placebo recipients. Thus, on the basis of these integrated SAE analyses, there was no evidence of a new safety concern in young children.

Special Population Issues

Persons With Asthma or Wheezing Illness

In several FluMist® trials involving patients with or without known asthma/wheezing or other respiratory tract disease, specific data were collected regarding asthma exacerbations and asthma stability, outcomes of interest that were pre-specified in the study protocol. These studies are discussed below.

In the large placebo-controlled study conducted at Northern California Kaiser Permanente (*study protocol AV019—Bergen 2004, Black 2002 & 2006*), there was an increased relative risk (RR 4.06, 90% CI: 1.29, 17.86) of medically attended asthma events in children 18 to 35 months of age (16 of 728 FluMist® recipients and 2 of 369 placebo recipients); 44% (7/16) of the FluMist® recipients who experienced events had a prior history of asthma or reactive airways disease. No hospitalizations for asthma occurred in FluMist® or placebo recipients (1 to 17 years of age). Most asthma and wheezing episodes were evaluated and treated in a single outpatient visit, usually with standard beta-agonist bronchodilators. In approximately 20% of cases, a short course of oral corticosteroids was needed.

In a placebo-controlled study in 48 children (9 to 17 years of age) with moderate to severe asthma, 2 asthma exacerbations were observed in the 24 FluMist® recipients and none in the 24 placebo recipients (*Redding 2002*). There was no difference in pulmonary function tests (e.g., FEV1, FVC), bronchodilator use, and asthma symptoms between the FluMist® and placebo groups. In a large placebo-controlled trial in healthy adults (N=4561) 18 to 64 years of age, a subset of 36 participants with a history of asthma was identified (*Nichol 1999*). Two of 23 (8.7%) FluMist® recipients and 1 of 13 (7.7%) placebo recipients with a history of asthma experienced wheezing within the 7 days following vaccination. None of the exacerbations required hospitalization.

Subsequently, 2 open-label studies enrolling approximately 2000 children each were conducted outside the United States comparing TIV and refrigerated FluMist®. One was Study D153-P514 (*Ashkenazi 2006*) in young children with recurrent respiratory tract infections; the other was Study D153-P515 (*Fleming 2006*) in asthmatics 6-17 years of age. Neither of these studies identified a statistically significant increase in wheezing or

FluMist® should not be administered to any individuals with asthma or to children <5 years of age with recurrent wheezing because of the potential for increased risk of wheezing post-vaccination unless the potential benefit outweighs the potential risk.

asthma exacerbations, and both showed higher efficacy of FluMist® compared with TIV (53% and 35% relative efficacy, respectively).

Based on these observations, pivotal Study MI-CP111 (*Belshe 2007*) was prospectively designed to evaluate asthma or wheezing from FluMist® (as identified earlier in AV019 study) vs. TIV ("flu shot") as the active control group. Given the difficulties with collection of wheezing outcomes in young children, a protocol case definition of wheezing ("medically significant wheezing," MSW) was established to allow direct comparison of a prospectively collected wheezing outcome between the 2 randomized treatment groups. To meet the case definition, a child was required to have a medical diagnosis of wheezing associated with other respiratory findings (e.g., hypoxemia, respiratory distress, or initiation of daily bronchodilator therapy within 42 days after vaccination). As seen in Table 22, wheezing was low for both FluMist® and TIV. A significant difference was seen in children 6 to 23 months of age. For the indicated FluMist® population aged 24 to 59 months, FluMist® had a slightly lower incidence rate than TIV. While the rates of protocol-defined wheezing (MSW) were different in FluMist® recipients younger than 24 months of age, severity of MSW episodes did not appear to be increased, and FluMist® and TIV recipients with MSW did not appear to have different rates of recurrent wheezing (i.e., 2 or more additional episodes). See Table 23. A similar age-related trend was seen for all-cause hospitalizations (discussed in further detail below).

Table 22.—Percentages of Children With Hospitalizations and Wheezing from Study MI-CP111

Adverse Reaction	Age Group	FluMist®	Active Control[a]
All-Cause Hospitalizations[b]	6-23 months (n=3967)	4.2%	3.2%
	24-59 months (n=4385)	2.1%	2.5%
Wheezing[c]	6-23 months (n=3967)	5.9%	3.8%[d]
	24-59 months (n=4385)	2.1%	2.5%

[a]Injectable influenza vaccine.
[b]From randomization through 180 days post last vaccination.
[c]Wheezing requiring bronchodilator therapy or with significant respiratory symptoms evaluated from randomization through 42 days post last vaccination.
[d]Statistically significant difference, 95% CI 0.72, 3.38.

Please see accompanying Full Prescribing Information (Package Insert).

Table 23.— Severity of Protocol-Defined Medically Significant Wheezing (MSW) in Children <24 Months of Age (from Study MI-CP111)

Characteristic	FluMist® N=117	TIV N=75
Respiratory Distress	26 (22%)	21 (28%)
Hypoxemia*	11 (9%)	7 (9%)
Respiratory Distress or Hypoxemia	29 (25%)	23 (31%)
New Bronchodilator Only	88 (75%)	52 (69%)
Two or More Additional Episodes	5 (4.3%)	4 (5.3%)
Hospitalized Protocol-Defined Wheezing	9 (7.7%)	3 (4.0%)
Duration of Hospitalization (days)	4.5	4

*Hypoxemia was measured only when clinically indicated.

Children Younger Than 24 Months of Age

Based on these studies, FluMist® should not be administered to any individuals with a history of asthma or to children <5 years of age with recurrent wheezing because of the potential for increased risk of wheezing post-vaccination (see package insert).

When analyzed by age subgroup, a statistically significant difference in the rate of all-cause hospitalization was observed for children 6 to 11 months of age through 180 days following last vaccination (6.1% FluMist®, 2.6% TIV). The majority of excess hospitalizations in this subset of younger children occurred late (occurred >42 to 180 days after receipt of final study vaccination), were not temporally clustered, and were events commonly expected to occur in a young pediatric population, i.e., gastrointestinal and lower respiratory tract infections. A biological rationale for an association between receipt of FluMist® and these late-occurring hospitalizations cannot be readily explained. In older subgroups of children 12 to 23 and 24 to 59 months of age, hospitalization rates were not increased in FluMist® vs. TIV recipients overall.

HIV-Infected Children and Adults

Limited data regarding the safety of vaccination with FluMist® in mildly immunosuppressed individuals are currently available. In controlled studies, FluMist®, when administered at the standard dose, was well tolerated in relatively asymptomatic children (n=24, aged 1 to 7 years) and adults (n=57, aged 18 to 58 years) infected with human immunodeficiency virus (HIV) (*King 2000 & 2001*). Prior to FluMist® vaccination, CD4 cell counts for these HIV-infected children and adults were mean 1114 cells/mm^3 (range 918 to 1353 cells/mm^3) and mean 598 cells/mm^3 (range 525 to 682 cells/mm^3), respectively. The mean baseline CD4% (of T-cells) was reported as 37% in the pediatric study (*King 2000*). Both children and adults had plasma HIV RNA polymerase chain reaction measurements less than 10,000 copies/mL and were in CDC Class N or A1-2. Results showed that FluMist® did not affect CD4 counts or HIV RNA concentrations, nor increase or prolong vaccine virus shedding compared with HIV-infected individuals who received placebo. In addition, these individuals did not shed vaccine viruses in higher titers or for a longer duration than healthy (HIV-negative) persons (*King 2000 & 2001*). Reactogenicity rates were similar in FluMist® and placebo recipients, except that runny nose/nasal congestion were significantly more common in FluMist® adult recipients regardless of HIV status (*King 2000 & 2001*). No serious adverse events were reported during the 1-month follow-up period.

It should be remembered that the attenuation and level of replication of FluMist® viral strains reduces the chance for causing influenza-like illness in close contacts.

—Murphy 2002

These findings were corroborated in a recent study of similarly affected HIV-positive children aged 5 to 17 years old (*Levin 2008*). Notably in this latest study (PACTG 1057), almost 90% of confirmed shedding of FluMist® vaccine virus occurred within 4 days after vaccination, with only 3 additional positive specimens on days 5 or 6 post-vaccination. There were no significant increases from baseline in median/mean plasma HIV viral load after either FluMist® or TIV vaccine in any of the immunologic groups. Similarly, CD4% did not change significantly at any time point as a result of vaccination. There number of subjects with adverse events was similar after either vaccine in all event categories except for the injection site reactions after TIV (23% overall) and more naso-pharyngeal symptoms after FluMist® compared with TIV (52% vs. 31%; p=0.002)

Pregnancy and Nursing Mothers

FluMist® has an FDA Pregnancy "Category C" rating. The safety of FluMist® in pregnancy has not been assessed prospectively. FluMist® or placebo was administered in clinical trials to 11 women who were later found to be pregnant or became pregnant soon thereafter. Two pregnancies terminated spontaneously (1 vaccinee and 1 placebo recipient), 8 resulted in delivery of healthy infants (7 in vaccinees and 1 in a placebo recipient), and 1 vaccinee delivered a pre-term infant (37-week gestation).

Animal reproduction studies have not been conducted with FluMist®. It is also not known whether FluMist® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. FluMist® should be given to a pregnant woman only if clearly needed.

Please see accompanying Full Prescribing Information (Package Insert).

The effect of FluMist® on embryo-fetal and pre-weaning development was evaluated in a developmental toxicity study using pregnant rats. Groups of animals were administered FluMist® either once (during the period of organogenesis on gestation day 6) or twice (prior to gestation and during the period of organogenesis on gestation day 6), 0.25 mL/rat/occasion (approximately 110-140 human dose equivalents based on $TCID_{50}$) by intranasal instillation. No adverse effects on pregnancy, parturition, lactation, or embryo-fetal or pre-weaning development were observed. There were no vaccine-related fetal malformations or other evidence of teratogenesis noted in this study.

It is not known whether FluMist® is secreted in human milk. Therefore, as some viruses are excreted in human milk, and additionally, because of the possibility of shedding of vaccine virus and the close proximity of a nursing infant and mother, caution should be exercised if FluMist® is administered to nursing mothers. According to recent CDC recommendations (*CDC/ACIP 2008*), "women who are breastfeeding may receive either TIV or LAIV unless contraindicated because of other medical conditions."

Persons With Chronic Underlying Medical Conditions

The safety of FluMist® in individuals with underlying medical conditions that may predispose them to complications following wild-type influenza infection has not been established. FluMist® should not be administered unless the potential benefit outweighs the potential risk (see WARNINGS & PRECAUTIONS in FluMist® package insert).

According to the CDC's Advisory Committee on Immunization Practices (ACIP), such individuals include, but are not limited to, adults and children with chronic disorders of the pulmonary and cardiovascular systems; pregnant women who will be in their second or third trimesters during influenza season; 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 (*CDC/ACIP 2008*).

Guillain-Barré Syndrome

The 1976 "swine flu" influenza vaccine (monovalent) was associated with an increased frequency of Guillain-Barré syndrome (GBS) (*Souayah 2007*). Among persons who received the swine influenza vaccine in 1976, the rate of GBS that exceeded the background rate was less than 10 cases/1 million persons vaccinated, with the risk for influenza-vaccine-associated GBS higher among persons 25 years of age and older (*CDC/ACIP 2002*). Evidence for a causal relation between subsequent vaccines prepared from other influenza viruses and GBS is unclear. Obtaining strong epidemiologic evidence for a possible limited increase in risk is difficult for such a rare condition as GBS, which has an annual incidence of 10 to 20 cases/1 million adults. Thus, investigations to date indicate no substantial increase in GBS associated with influenza vaccines (other than the swine influenza vaccine in 1976), and that if influenza vaccine does pose a risk, it is probably slightly more than 1 additional case/1 million persons vaccinated. Cases of GBS after influenza infection have been reported, but no epidemiologic studies have documented such an association (*CDC/ACIP 2008*). No confirmed cases of GBS were reported in clinical trials for FluMist®. With approximately 10 million FluMist® doses distributed to date, the number of GBS cases post-FluMist® is within the background rate of the general population.

The incidence of GBS among the general population is low, but persons with a history of GBS have a substantially greater likelihood of subsequently experiencing GBS (*CDC/ACIP 2008*). Thus, the likelihood of coincidentally experiencing GBS after influenza vaccination is expected to be greater among persons with a history of GBS than among persons with no history of this syndrome. If Guillain-Barré syndrome has occurred within 6 weeks of any prior influenza vaccination, the decision to give influenza vaccines such as FluMist® or TIV should be based on careful consideration of the potential benefits and potential risks (*CDC/ACIP 2008, FluMist® 2008 Package Insert*).

Person-to-Person Transmission

FluMist® contains live attenuated influenza viruses that subclinically infect and replicate in cells lining the nasopharynx of the recipient so as to induce immunity. Vaccine viruses capable of replication can be cultured from nasal secretions obtained from vaccine recipients in the first few days after vaccination. The relationship of viral replication in a vaccine recipient to transmission of vaccine viruses to other individuals has not been established. Cold-adapted influenza viruses that were forerunners of FluMist® have been shown to be poorly transmissible under a variety of circumstances in small trials to spouses, roommates, and household members (*Murphy 2002*).

The likelihood that FluMist® vaccine viruses would be transmitted from a vaccinated individual to a non-vaccinated individual under "worst-case conditions" was the primary objective of a prospective, randomized, double-blind, placebo-controlled trial (Protocol #D145-P500; see Table 7) (*Vesikari 2006b*). A child day care center was specifically chosen to

enhance the probability of detecting transmission events, because young children are known to shed vaccine virus at higher titers and for longer duration than older children or adults (*Murphy 2002*) (see Figure 9). Children enrolled in the study attended day care at least 3 days per week for 4 hours per day and were in a playroom with 4 or more children, at least 1 of whom was vaccinated with FluMist®.

A total of 197 children 8 to 35 months of age were randomized to receive 1 dose of FluMist® (n=98) or placebo (n=99). Virus shedding was evaluated for 21 days by culture of nasal swabs obtained from each subject approximately 3 times per week.

Eighty percent of FluMist® recipients shed at least 1 vaccine strain, with a mean duration of shedding of 7.6 days (range 1-21 days). However, transmission of vaccine viruses from vaccinees to placebo subjects was a rare event. The cold-adapted (*ca*) and temperature-sensitive (*ts*) phenotypes were preserved in all recovered viruses tested (n=135 tested; of 250 strains isolated at the local laboratory). One type B isolate from 1 placebo recipient was confirmed to be vaccine virus. (This isolate retained the *ca*, *ts*, and attenuated [*att*] phenotypes of the vaccine strain and had the same genetic sequence when compared with a type B virus shed by a vaccine recipient within the same playgroup.) This placebo recipient experienced cough, coryza, and irritability similar to the symptoms observed among some FluMist® vaccinees in the trial. Wild-type A (H3N2) influenza virus was documented to have circulated in the community and in the study population during the trial, whereas type A (H1N1) and type B strains did not. Type A virus that could not be further characterized as vaccine or wild-type virus was isolated from 4 additional placebo recipients.

Assuming that only a single transmission event occurred (i.e., isolation of the type B vaccine strain), the probability of a young child acquiring vaccine virus following close contact with a single FluMist® vaccinee in this day care setting was 0.58% (95% CI: 0, 1.7) based on the Reed Frost model (*Longini 1982*). (The Reed Frost model assumes that the probability of a transmission event is related to the number of exposures to vaccine recipients.) With documented transmission of type B virus in 1 placebo subject and possible transmission of type A virus in 4 placebo subjects, the maximum probability of acquiring a transmitted vaccine virus was estimated to be 2.4% (95% CI: 0.13, 4.6), using the Reed Frost model.

The duration of FluMist® vaccine virus replication and the potential for transmission of vaccine viruses by recipients to bystanders have not been established but continue to be studied in the postlicensure phase. For a more in-depth analysis of combined pre-licensing and post-licensing shedding/transmission data, see Chapter V. In any case, researchers have noted that the attenuation and low level of replication of FluMist® minimizes the chance for causing influenza-like illness in close contacts (*Murphy 2002*).

Adverse Event Reporting—VAERS

The Vaccine Adverse Event Reporting System (VAERS) is a national program jointly managed by the U.S. FDA and CDC that monitors the post-marketing safety of vaccines. Adverse events reported by health care providers or patients are received and recorded by VAERS. In addition, manufacturers are required to submit all adverse event reports they receive to VAERS. The VAERS toll-free number is 1-800-822-7967. Reporting forms may also be obtained at the FDA Web site at: *http://www.vaers.hhs.gov*. MedImmune Vaccines, Inc also actively collects and reports adverse events to VAERS in conjunction with their postmarketing pharmacovigilance program.

No causal relationship can be determined from VAERS data (*FDA-CDC 2005*); the data are used primarily to identify or signal a problem involving rare events not readily observed in clinical development trials. For a detailed discussion of VAERS post-marketing data recently reported for FluMist®, see the Safety and Efficacy section in Chapter V (Post-Marketing and Related Studies).

Warnings and Contraindications

Under no circumstances should FluMist® be administered parenterally. FluMist® should only be given by nasal administration. Please refer to the FluMist® package insert for the warnings statements and a description of contraindications and/or patient types that should not receive FluMist®.

Please see accompanying Full Prescribing Information (Package Insert).

V. Post-Marketing and Related Studies

Additional studies were performed for evaluation of cross-reactive antibody responses (against antigenically "drifted" strains), cost-benefit analysis, shedding/transmission data, and further safety and efficacy data. Relevant findings are reviewed below. Other FluMist studies currently in progress can be viewed at *www.clinicaltrials.gov*.

Cross-Reactive Antibody Responses (Vaccine Mismatch)

Since earlier pilot studies had suggested LAIV vaccines could protect against antigenically drifted influenza strains (*Clover 1991, Edwards 1994*), and this was clinically demonstrated in the 1997-1998 season of the pivotal AV006 Pediatric Efficacy Study, serum specimens obtained during the first year (1996-1997) of this study were tested in the laboratory for HAI (hemagglutination-inhibition) antibodies against a variety of mismatched A/H3N2 strains isolated during the influenza seasons immediately preceding or after this trial (*Belshe 2000a, 2003, & 2004*). These specimens were compared with the serum of younger children who were immunized with injectable trivalent inactivated vaccine (TIV) containing the same H3N2 strain (A/Wuhan/359/95, which is Nanchang-like antigen) used in FluMist® that season (1996-1997). Results of the analysis indicated that children who were vaccinated with FluMist® developed significantly higher serum HAI antibodies that cross-reacted with all 4 of the drifted H3N2 strains (see Figure 13). For the vaccine-matched strain (Nanchang-like antigen), both TIV and FluMist® had equally high HAI antibody, as would be expected.

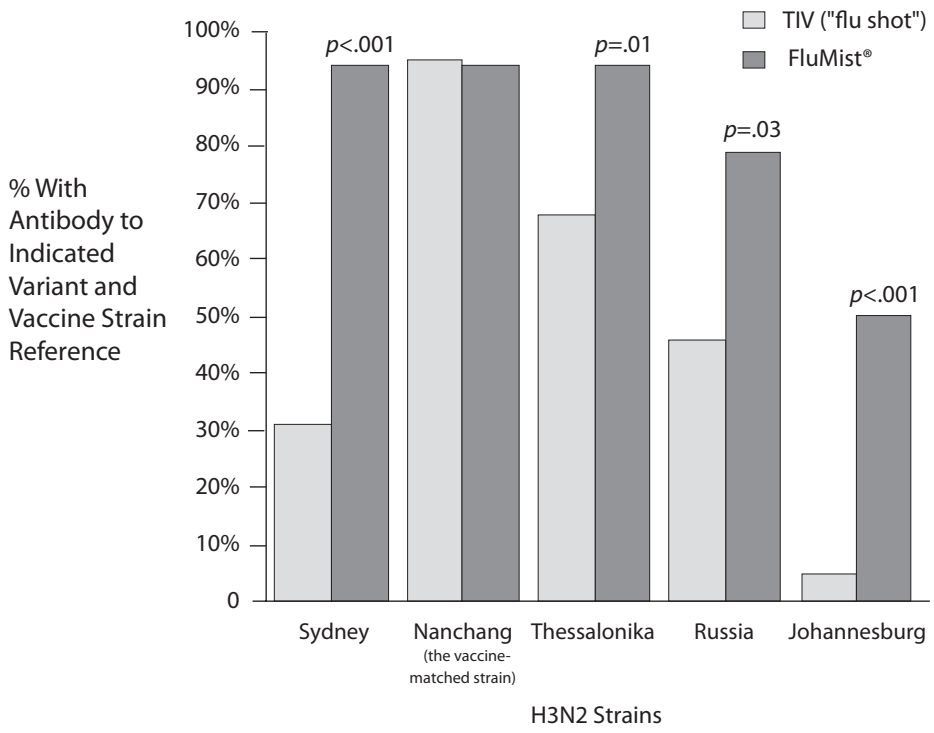

Figure 13.—Percentage of children given 2 doses of FluMist® (dark bars) or 2 doses of TIV (light bars) with HAI antibody post-vaccine to the indicated variant strain of type A/H3N2. (Reprinted from *Virus Research*, Vol 103, Belshe, Current status of live attenuated influenza virus vaccine in the US, page 181, ©2004, with permission from Elsevier.)

In the 2003-2004 influenza season, the predominant influenza strain in US circulation was a drifted strain of A/H3N2 (*CDC/ACIP 2004*). Only 11% of the A/H3N2 viruses antigenically characterized by the CDC from patient specimens were similar to the vaccine strain (A/Panama/2007/99), while 89% were similar to the drifted strain, A/Fujian/411/2002 (see Table 3) (*CDC/ACIP 2004*). Likewise, the 2004-2005 season had a 78% mismatch (A/Wyoming/3/2003) for the A/H3N2 vaccine strain (A/California/7/2004-like). Thus, 2 pilot studies were conducted in children (with refrigerated FluMist®) to determine the level of vaccine cross-protection (A/California/7/2004-like).

The immunogenicity of a single dose of FluMist® or trivalent inactivated influenza vaccine (TIV) against a drift variant was retrospectively evaluated using frozen sera from seronegative children (age 6 to 36 months) who had been vaccinated prior to the 2001-2002 influenza season with vaccines containing the A/Panama/2007/99 (H3N2) strain (*Mendelman 2004*). In 2003, frozen sera collected from these children during the 2001-2002 study were evaluated for heterotypic cross-reactivity against the drifted A/Fujian/411/2002-like A/H3N2 strain (A/Wyoming/03/2003). Neutralizing or hemagglutination-inhibiting (HAI) antibody responses were defined as greater than or equal to a 4-fold rise in antibody titer from baseline. Sera were obtained prior to and 28 days after vaccination and analyzed for HAI and neutralizing antibody titers using standard assays. A greater percentage of FluMist® (20%) than TIV (4%) recipients had HAI responses to the drifted strain, although the difference was not statistically significant (p=0.09). However, a significantly greater percentage of FluMist® (67%) than TIV (4%) recipients had neutralizing antibody responses to the drifted strain (p<0.0001) (*Block 2004, Mendelman 2004*).

Please see accompanying Full Prescribing Information (Package Insert).

In a follow-up study (MI-CP123) of a subset of patients from the MI-CP111 pivotal clinical trial, 52 children aged 6 to 35 months who received 2 doses of FluMist® (n=24) or TIV (n=28) in the 2004-2005 season were assessed for serum HAI responses to the 3 vaccine-like (matched) and 2 mismatched strains that circulated that season (*Belshe 2006*). Geometric mean titers of HAI were significantly higher in seronegative FluMist® vs. TIV recipients after both dose 1 and dose 2 in most strains (see Table 24).

Shedding/Transmission

The CDC recently stated, *"Available data indicate that both children and adults vaccinated with LAIV can shed vaccine viruses after vaccination, although in lower amounts than occur typically with shedding of wild-type influenza viruses. In rare instances, shed vaccine viruses can be transmitted from vaccine recipients to unvaccinated persons. However, serious illnesses have not been reported among unvaccinated persons who have been infected inadvertently with vaccine viruses"* (*CDC/ACIP 2008*).

In order to expand the analysis of shedding and transmission data from the Finnish Daycare Study (Protocol # D145-P500/*Vesikari 2006b;* see Table 7) reported in the BLA, a post-hoc review of available nasopharyngeal specimens from subjects in other pre-licensure clinical trials of FluMist® was undertaken (*Stoddard 2004*). The review included 159 subjects in 3 pediatric studies (AV002, D145-P500, and DMID 99-012) and 85 subjects in 3 adult studies (DMID 98-005, D145-P501, and AR001) (as referenced in Table 7). As seen in Table 25, no study had a shedding rate as high as the Finnish Daycare Study nor a duration exceeding 10 days. Findings were similar for mild-to-moderate immunosuppressed HIV-infected populations.

Subsequent to this review, a post-marketing adult study from the 2003-2004 influenza season was reported (*Talbot 2005*). Twenty volunteer subjects (18-49 years old, mean age 32 years old) had a nasal wash sampling at 4 time points after receiving FluMist® vaccination (on days 3, 7, and 10 and between days 17 to 21). Influenza shedding was seen in 50% (10/20) of subjects on day 3, 5.5% (1/18) of available specimens on day 7, and none of the specimens from day 10 (0/19) or days 17 to 21 (0/20). The specific influenza strain detected varied, with 3/11 (27%) cultures positive for influenza type A alone, 5/11 (45%) positive for influenza type B alone, and 3/11 (27%) positive for both influenza A and B strains. Persons with a positive nasal wash culture were significantly younger than those who did not shed (mean age 26.4 years old in those with a positive culture versus 38.6 years old in those without shedding, $p<0.01$).

Table 24.— Study MI-CP123: HAI Response in Seronegative Infants

Vaccine strains shown in bold *Mismatched strains* shown in italics	**Geometric Mean Titers**					
	FluMist®			**TIV**		
	Pre	**Dose 1**	**Dose 2**	**Pre**	**Dose 1**	**Dose 2**
A/New Cal (H1N1)[a]	<4	7.4[b]	34.7[b]	<4	<4	<4
A/Wyoming (H3N2)[a]	<4	121.4[b]	93.0[b]	<4	4.3	26.3
A/California (H3N2)	<4	21.5[b]	12.9[b]	<4	<4	<4
B/Shanghai	<4	12.7[b]	17.3	<4	4.5	11.9
B/Florida	<4	8.6	14.9	<4	4.0	9.2

[a]Results using cold-adapted antigens; further testing with wild-type antigens in progress.
[b]Statistically significant vs. TIV ("flu shot").

Table 25.— FluMist® Isolation/Detection in Healthy and HIV-Infected Populations

Healthy Populations								
Study	**Age Range**	**Mean Age[a]**	**Days Evaluated**	**Number of Cultures Taken**	**Number of Subjects Evaluated**	**Percent Who Shed on Any Day**	**Last Day Shed**	**Percent Who Shed on Last Day**
Children								
Wyeth D145-P500 (*Vesikari 2006b*) "The Finnish Daycare Study"	8-36 months	27 months	0-21 QOD	12	98	80	21	1[b]
AV002/002-2 (*King 1998*)	18-71 months	44 months	1-2, 3-6, 7-10	3	36	78	7-10[c]	47
DMID 99-012 (*King 2001*)	1-7 years	4.3 years	3-5, 7-10, 28-35	3	25	28	7-10[c]	12
Adults								
DMID 98-005 (*King 2000*)	18-50 years	35 years	3-5, 7-10, 28-35	3	27	0	None	0
Wyeth D145-P501 (*unpublished*)	20-44 years	24 years	1-6	6	30	23	6	3
AR001 (*unpublished*)	22-59 years	39 years	0, 3	2	28	21	3	21

HIV-Infected Populations								
Study	**Age Range**	**Mean Age[a]**	**Days Evaluated**	**Number of Cultures Taken Evaluated**	**Number Subjects Day**	**Percent Who Shed on Any**	**Last Day Shed**	**Percent Who Shed on Last Day**
DMID 99-012	1-7 years	5 years	3-5, 7-10, 28-35	3	23	13	7-10[c]	4
DMID 98-005	27-52 years	40 years	3-5, 7-10, 28-35	3	28	4	3-5	4

[a]Mean age as a whole.
[b]Few children had virus isolated after day 14: 0% shed on day 9-10; 9% on day 11-12; 0% on day 13-14; 2% on day 15-16; 1% on day 17-18; and 0% on day 19-20.
[c]Time point measured was once during days 7-10.

All of these data are consistent with the results of previously published NIH studies with FluMist® precursors in which peak titers of vaccine viruses in respiratory secretions were lower and the duration of virus replication was shorter in adults (approximately 7 days) than children (*Murphy 2002*). The risk of transmission is low even in a high-probability risk scenario (i.e., among young children in a day care setting).

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Safety and Efficacy

Post-Marketing Safety (VAERS)

As part of ongoing FDA post-marketing surveillance, VAERS collects data on any adverse event following vaccination (be it coincidental or truly caused by a vaccine). As such, VAERS advises that for any reported event, no cause and effect relationship has been established. VAERS published a report of the first 2 years post-licensing experience (August 1, 2003 to July 31, 2005) involving an estimated 2.5 million FluMist® recipients (*Izurieta 2005*). The objective of the study was to "describe the characteristics of reported adverse events and to identify new or unexpected adverse events, including rare events." They received a total of 460 adverse events (ADE) reports (or a report rate of 0.184 per 1,000 recipients), with 40 judged as "serious"; no deaths occurred in any report.

The events of primary interest to VAERS were identified in premarketing clinical trials or reported with other influenza vaccines. They included neurological events, anaphylaxis, secondary transmission of vaccine strains to contacts, influenza-like illness, and asthma. The findings for these primary areas are reviewed below.

Neurological Events

There were 3 reports involving Guillain-Barré syndrome (GBS), but 1 lacked any supportive information and was excluded from further analysis. Both of the remaining 2 cases were confirmed by a neurologist. In 1 case, the interval between the FluMist® administration and onset of GBS was considered too short for a causal relationship, and the subject in the other case had a concurrent upper respiratory illness as an alternative non-vaccine etiology. There was 1 case of Bell's palsy. The onset was within 5 days post vaccination, and no cause was identified, although the patient had a prior episode of Bell's palsy 20 years ago.

Anaphylaxis

Out of a total of 460 adverse events (ADE) reported, 7 involved anaphylaxis. None of the patients had a history of a vaccine allergy, but 5 subjects did report a history of hypersensitivity, including contact dermatitis and drug and seasonal allergies. Only 1 event was considered serious, and none required hospitalization. In all cases, the onset was within 3 hours, and in 5 cases, within 20 minutes. This rate of reporting (2 per million) was well within the range observed by the Institute of Medicine for anaphylaxis after measles-mumps-rubella vaccination, and somewhat higher than the 0.65 cases per million doses reported for all childhood and adolescent vaccinations in 4 health maintenance organizations.

Secondary Transmission

Out of a total of 460 adverse events (ADE) reported, 22 were for suspected secondary transmission. There were no reports of transmission to immunocompromised patients and no hospitalizations. Viral cultures were performed at the CDC laboratories in one case of a 4-year-old child of a vaccinated pediatrician who developed symptoms 15 days after vaccination. The cultures revealed isolates that were circulating wild-type A (H3N2) and did not contain any gene of the FluMist® strains. No specimens were available for viral culture from the other 21 suspected cases. Viral culture confirmation is vital to establish secondary transmission, and as noted by the authors, "In the absence of viral characterization, reports of possible secondary transmission events may represent coincidental, naturally occurring respiratory infections." Finally, the authors of the editorial that accompanied the VAERS report concluded, "These and other studies substantiate the current recommendations that LAIV is safe for close contacts of high-risk patients except the most highly immunocompromised, such as hematopoietic stem cell transplant recipients receiving care in protected environments (*Neuzil 2005*)." (See Table 4 in Chapter 2 for details on CDC recommendations.)

FluMist® vaccine contains the core (internal) influenza virus proteins—a distinct product feature—and the same major surface antigens (hemagglutinin and neuraminidase) as the injectable trivalent inactivated influenza vaccine (TIV).

Influenza-like Illness (ILI)

ILI events were defined as fever and cough possibly related to influenza, unless diagnosed otherwise. There were 67 reports of suspected ILI, and none of these resulted in hospitalization.

Asthma

Out of a total of 460 adverse events (ADE) reported, 12 cases involved asthma. Nine of the reports were in children 6 to 15 years of age and 3 in adults. Eight of the cases were among patients with a history of asthma. (Note—the FluMist® package insert advises, "FluMist® should not be administered to any individuals with asthma and children <5 years of age with recurrent wheezing because of the potential for increased risk of wheezing post-vaccination.") The interval from vaccination to symptom onset ranged from a few hours to more than a month. In 6 asthma events, the interval was 4 days or less.

Placebo-Controlled Efficacy of FluMist® Versus TIV in Adults

A clinical trial in adults comparing FluMist®, TIV ("flu shot"), and placebo was reported from the 2004-2005 and 2005-2006 influenza seasons (*Ohmit 2008*). Measured endpoints in the study were laboratory-confirmed, symptomatic influenza type A or B illness verified in patients by culture, polymerase chain reaction (PCR) testing of throat swab specimens, and/or serologic lab confirmation, defined as a rise from baseline pre-study serum levels of >4-fold IgG antibody titer for HAI. The primary analysis was "absolute efficacy" (i.e., placebo comparison), and the secondary analysis was "relative efficacy" (vaccines comparison). Safety outcomes were also assessed as a secondary objective.

Assuming a placebo influenza attack rate of 5% in the community, the investigators stated at least 1800 evaluable subjects would be required. As it turns out, only 1247 adults were enrolled for virus isolation and PCR analyses, and only 876 subjects had suitable specimens for per-protocol analyses of serology. The under-powering of the study substantially reduced

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its statistical analysis. Given the statistical limitations of sample size, none of the comparisons between FluMist® or TIV could be generalized or considered conclusive (*Fukuda 2006*).

Absolute efficacy for all strains combined was 67% to 77% for TIV and 30% to 57% for FluMist® based on the 3 primary analyses (culture, culture or PCR, and culture or serology) for laboratory-confirmed symptomatic influenza. TIV was significantly better than placebo across all 3 analyses, while none of the FluMist® findings were statistically significant. When the efficacy of TIV was compared with FluMist® (for all strains combined), TIV was 45% to 70% more efficacious based on the 5 reported categories for "laboratory-confirmed symptomatic influenza". However, only the serologic positive estimate of efficacy (70%) was statistically significant. The investigators concluded that ***"the estimation of relative efficacy did not indicate a significant advantage of TIV over LAIV."***

In the assessment of absolute efficacy against influenza type A strains (which were predominately drifted in the 2004-2005 national season), both TIV and FluMist® showed positive point estimates of 74% vs. placebo for the culture positive cases but neither of these findings met statistical significance. A higher point estimate was seen for TIV compared with FluMist® when PCR was added to define cases (69 vs. 47%) but this difference was also not significant.

In the assessment of absolute efficacy against influenza type B strains, TIV showed statistically significant efficacy (80%-83%) versus placebo for culture positive with or without PCR endpoints. Although trending favorable, the absolute efficacy of FluMist® (40%-49%) did not meet statistical significance. Likewise, for relative efficacy (67%), TIV versus FluMist® was not statistically significant for both culture and culture + PCR endpoints.

Runny nose or congestion, cough, headache, and muscle aches were statistically increased in FluMist® recipients versus nasal placebo. Side-effect symptom frequencies reported by FluMist® recipients peaked on days 2 through 4 post-vaccination. Arm soreness was statistically increased in TIV recipients versus injectable placebo.

The second year of this study was conducted during the 2005-2006 influenza season when the influenza season was late and of low intensity (*Ohmit 2008*). A total of 2058 persons were randomized to TIV (n=867), FluMist® (n=853) or placebo (n=338) and vaccinated in October and November 2005. The primary circulating influenza strain was type A (H3N2) that was antigenically similar to the H3N2 component of the vaccine. The efficacy of the vaccine against the B strain could not be determined because too few strains were identified. Absolute efficacy of TIV was 16% (95% CI: -171 to 70) for the virus identification endpoint (i.e., virus isolation in cell culture or identification through polymerase chain reaction) and 54% (95% CI: 4 to 77) for the primary endpoint (virus isolation or increase in serum antibody titer). The absolute efficacies of FluMist® for these endpoints were 8% (95% CL: -194 to 67) and 43% (95% CI: -15 to 71) respectively. However, the absolute efficacies for TIV and FluMist® for cultured confirmed influenza were 23% (95% CI: -153 to 73) and 61% (95% CI: -48 to 89), respectively. The study was limited by an influenza attack rate of only 1.8% in the placebo group. Given the lower than expected attack rate for these endpoints, the authors concluded that the study was underpowered to measure statistically significant vaccine efficacy.

School-Mist Trials

Building on a pilot study published earlier (*King 2005*), in which a cluster of 185 school children was vaccinated with FluMist® to reduce the spread of influenza in households and communities via "herd immunity," King et al. subsequently reported findings from a trial involving 28 schools (*King 2006*).

Rather than randomizing individual students, schools were grouped into 11 clusters and 7 of these 11 were randomized to receive either FluMist® or observation alone (the study defined these clusters as 1 "intervention" school where FluMist® was offered, and 1 to 2 "control" schools where no vaccine was offered per cluster). Control schools were matched with respect to geographic characteristics, students' ethnic background, and socioeconomic status. In the 4 other clusters, the intervention school was designated by the school administrators.

Subjects were 5 to 14 years of age (mean age, 7.9 ± 2.08 years), from 24 public elementary schools in Maryland, Texas, and Minnesota, and 4 parochial schools in Washington. Children were vaccinated according to product label in the fall of 2004. A total of 2717 children from the target intervention schools received FluMist® (for a vaccination rate of 46%). The primary objective of the study was to assess the effect of a school-based vaccination program on the households of children attending the schools (primarily using a household questionnaire completed by their parents). The secondary objective was to assess school absences (using administrative data collected by the schools). Data were collected by questionnaire survey of households at or near the peak of influenza activity in each community. Seventy-seven percent and 83% of questionnaires were returned by households with children in intervention schools and control schools, respectively.

Findings from the study are shown in Table 26. Compared with control-school households, intervention-school households had significantly fewer influenza-like symptoms and outcomes during the peak influenza period. Furthermore, households with children in intervention schools reported significantly lower absentee rates for influenza-like illness among students in elementary school ($P<0.001$) and high school ($P=0.03$), and significantly fewer workdays that were missed by parents to care for their own, or someone else's, influenza-like illness ($P= 0.04$).

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Table 26.— Primary Analysis of Rates of Reported Use of Health Care and Medication, Missed Workdays, and School Absences Due to Fever or Influenza-like Illness During the Peak Influenza Week, as Reported on the Household Questionnaire.[a] (reprinted from King 2006b)

Outcome	Intervention Schools (FluMist®)	Control Schools	Adjusted Absolute Difference (95% CI)	*p* Value
Fever or influenza-like illness				
Total no. of households	3022	5,488	—	—
Children—no. (%)				
Any fever or influenza-like illness	1220 (40)	2,874 (52)	10.9 (8.4 to 13.3)	<0.001
Fever plus cough or sore throat[b]	512 (17)	1,446 (26)	8.3 (6.3 to 10.2)	<0.001
Adults—no. (%)				
Any fever or influenza-like illness	979 (32)	2,429 (44)	10.8 (8.0 to 13.6)	<0.001
Fever plus cough or sore throat[b]	253 (8)	710 (13)	3.7 (2.3 to 5.2)	<0.001
Use of health care				
Children—total no.	7892	14,017	—	—
Type of care—rate per 100 persons				
Outpatient (doctor's office or clinic)	7.27	11.37	3.39 (2.16 to 4.62)	<0.001
Emergency department or urgent care	1.03	1.32	0.24 (-0.22 to 0.70)	0.31
Inpatient	0.27	0.10	-0.13 (-0.25 to -0.01)	0.03
Adults—total no.	6046	11,080	—	—
Type of care—rate per 100 persons				
Outpatient (doctor's office or clinic)	4.96	6.70	1.12 (-0.04 to 2.28)	0.06
Emergency department or urgent care	0.89	0.97	-0.21 (-0.66 to 0.24)	0.36
Inpatient	0.20	0.13	-0.13 (-0.27 to 0.00)	0.05
Type of treatment				
Prescription—rate per 100 persons	7.27	11.70	3.71 (2.46 to 4.95)	<0.001
Over-the-counter—rate per 100 persons	17.43	25.26	7.71 (6.20 to 9.20)	<0.001
Vitamins or herbal remedies—rate per 100 persons	7.05	11.06	4.38 (3.06 to 5.69)	<0.001
Vaporizers or humidifiers—rate per 100 persons	4.39	5.88	1.69 (0.68 to 2.69)	0.001
School absence				
Any school-age children—rate per 100 persons	4.34	6.63	2.00 (1.27 to 2.73)	<0.001
Elementary school students	4.37	7.00	2.35 (1.44 to 3.26)	<0.001
Middle school students	5.23	6.10	0.36 (-0.10 to 0.81)	0.63
High school students	3.46	5.75	1.73 (0.21 to 3.24)	0.03
Paid workdays missed by adults				
For any fever or influenza-like illness or to care for children with fever or influenza-like illness—mean no. of days	0.292	0.388	0.07 (0 to 0.14)	0.04
To care for sick child[c]—mean no. of days	0.202	0.264	0.05 (-0.01 to 0.10)	0.09

[a] The questionnaire was administered immediately after the predicted peak influenza week. Calculations of adjusted absolute differences and *p* values were based on a mixed-effects model, including random school and cluster effects and controlling for differences between states. Dashes denote that data are not applicable.

[b] The responses were from households reporting 1 or more children or adults with fever and 1 or more children or adults with either cough or sore throat.

[c] The responses were only from households in which no adults ordinarily stayed home during the school day.

Our findings suggest that school-based immunization programs are cost-neutral after the peak week alone and cost-saving over an influenza season.

—Schmier 2008

We determined that because of the lower rates of influenza among children vaccinated with LAIV, 4346 cases of uncomplicated influenza and 1225 cases of complicated influenza can be avoided for every 100,000 children vaccinated with LAIV relative to TIV. The estimated cost savings amounts to $4.58 million for every 100,000 children vaccinated with LAIV relative to TIV.

—Luce 2008

No serious adverse events related to FluMist® were observed in the School-Mist trials. The authors concluded that "*Our multicenter study … demonstrates that school-based immunizations against influenza directly and indirectly reduce outcomes related to influenza-like illness.*"

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VI. Pharmacoeconomic Evaluation

Several studies have recently examined the cost effectiveness of influenza vaccination in children. Some of these studies are based directly on clinical trial data (*Esposito 2006, Hibbert 2007, Luce 2001 & 2008, Pisu 2005, Schmier 2008*), whereas others involve estimates of attack rates & vaccine efficacy from multiple published sources (*Cohen and Nettleman 2000, Marchetti 2007, Meltzer 2005, Prosser 2006, Salo 2006, Skowronski 2006, White 1999*). The studies vary considerably in the estimated seasonal influenza attack rates, proportion of children requiring 2 doses of vaccine, vaccine costs, and inclusion of secondary influenza transmission. All of these studies have found influenza vaccination to be potentially cost effective and, in some instances, a cost-saving option in the clinical management of children (*Cohen and Nettleman 2000, Esposito 2006, Hibbert 2007, Luce 2008, Meltzer 2005, Salo 2006, Schmier 2008, Skowronski 2006, White 1999*).

A growing number of pharmacoeconomic studies have specifically examined the economics of FluMist® (see Table 27). Models were developed using data from the pivotal FluMist® pediatric and adult clinical trials, AV006, CP111, and AV009, respectively (*Luce 2001, Luce 2008, Nichol 2001 & 2003*). In addition, economic evaluations of mass FluMist® vaccinations studies occurring outside the clinical setting, such as day care centers (D153-P502) and schools (SchoolMist), were performed (*Hibbert 2007, Schmier 2008*).

Pediatric Studies

The 2-year study period of the FluMist® pivotal trial (AV006) found that vaccinated children had an average 1.2 fewer days with febrile (>102˚F) influenza-like illness (ILI) symptoms (*Belshe 1998 & 2000a*). Based on this study (AV006), the direct and indirect costs were estimated for both an individual office-based vaccination scenario and a group vaccination scenario. This study was conducted from a societal perspective (*Luce 2001*). For each analysis, it was assumed that children were influenza vaccine naïve and therefore required 2 doses in the first year and only one per annum thereafter (as per package insert recommendation for dosing of new patients 5 to 8 years of age).

At an assumed cost of $20/dose for vaccine and administration, Luce et al. estimated a cost of $30/febrile ILI day avoided (range $10 to $69/febrile ILI day avoided at $10 to $40/dose administered, respectively). In a group vaccination scenario, FluMist® was estimated to be cost saving versus not vaccinating children, when the vaccine cost was under $28 (*Luce 2001*). This study suggests that vaccination of young children with LAIV would provide economic benefit. This benefit could be maximized if vaccinations were performed on a greater scale such as schools or vaccine clinics.

The economic analysis of the MI-CP111 clinical trial evaluated the relative cost and effectiveness of children aged 24 to 59 months who received either TIV or LAIV (*Luce 2008*). Based upon the clinical endpoints derived from the clinical trial, the economic model estimated that vaccination with LAIV could increase vaccination costs by $7.72 per child compared with TIV. However, compared with TIV, the clinical trial found that LAIV reduced the number of influenza illness cases, which was assumed to subsequently lower health care use in children and productivity loss of parents. LAIV was calculated to result in a net total cost savings of $45.80 per child relative to TIV.

The results of our study show that vaccination of children who attend day-care with FluMist® nasal spray vaccine is safe and effective and may be cost saving…

—Hibbert 2007

This cost benefit analysis based on the results of the FluMist® trial provides additional evidence that influenza vaccination may provide both health and economic benefits for healthy, working adults.

—Nichol 2003

Among working adults, influenza causes substantial suffering, decreased work productivity, and increased health care use.

—Nichol 2003

Both probabilistic and one-way sensitivity analyses were run and the results suggest that the findings from this economic analysis are quite robust. Since this model was based upon the clinical findings from MI-CP111, a single-season prospective, active-controlled, RCT efficacy trial, the generalizability of the findings are limited to the population studied and influenza season studied.

Additional economic studies were conducted alongside a couple of other recently completed clinical trials. These cost-effectiveness studies used data captured from Study D153-P502 (day care–based study) and the SchoolMist (school-based) study, which examined vaccinating outside the normal physician office–based setting. The P502 and SchoolMist economic evaluations both found vaccinating children outside the physician office to potentially be a cost-savings option (*Hibbert 2007, Schmier 2008*).

The effectiveness of vaccinating children with FluMist® in a day care setting was previously reported (*Vesikari 2006*). In a cost-effectiveness study using results from D153-P502, there was an overall societal cost savings of $5.47 and $144.44 in seasons 1 and 2, respectively (*Hibbert 2007*). The higher savings during the second influenza season are a consequence of a high attack rate in season 2 and the fact that children were no longer vaccine naïve in year 2, and thus required only a single dose of vaccine.

A published study on school-based influenza vaccination programs reported on an interventional, multistate, cluster-controlled trial involving more than 15,000 school children (*King 2006*). The intervention study found a significant reduction, during the peak week of influenza infection, in the percentage of households that had an individual report of influenza-like illnesses (ILI). The percentage of households where children experienced ILI (17% vs. 26%) as well as the households with sick

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adults (8% vs. 13%) were lower in the intervention school compared with the control schools. Vaccination costs along with the direct and indirect costs associated with influenza illness were incorporated in the model. During just the peak influenza week alone, the costs per household of a school-based immunization program was estimated to be equivalent to the savings associated from reduced influenza during the peak week alone ($163.76 vs. $163.05, respectively). Projecting over the entire season, the total difference in cost between the households from the intervention and control schools was estimated to be a savings of $171.96 (*Schmier 2008*).

Another case in point is the recently published study that evaluated the value (i.e., benefits and risks) of vaccinating children against influenza virus (*Prosser 2006*). They reported that in children 6 months to 17 years old without high-risk medical conditions, the use of FluMist® was estimated to cost less to prevent an influenza case, an influenza-related hospitalization, or an influenza related death than the use of TIV. In addition, their economic model found FluMist® had lower cost-effectiveness ratios than TIV [e.g., range: $3,000-$10,000 less per saved quality-adjusted life year (QALY)] in all age cohorts modeled (e.g., 2 years, 3-4 years, 5-11 years, and 12-17 years of age). The primary driver for the economic advantage associated with FluMist® was the difference in vaccine efficacy used in the model (0.838 vs. 0.69, FluMist® and TIV, respectively).

Adult Studies

In the Adult Effectiveness Study (*AV009—Nichol 1999*), Nichol incorporated the clinical trial findings into a cost-benefit analysis. Outcomes that were included in this cost-benefit analysis were days of work missed, days of reduced work effectiveness, and days with a health care provider visit due to influenza-like symptoms (*Nichol 2001 & 2003*). National payment data were used to estimate the cost of physician visits and medications. LAIV was found to be an effective and safe vaccine in healthy working adults, and this occurred even during a season of poor match between the circulating and vaccine virus strains. Over the 5-month outcome period, vaccination with FluMist®

- Lowered days of missed work by 18% (RR 0.82; p=0.0002)
- Lowered days of reduced work effectiveness by 18% (RR 0.82; p=0.0003)
- Lowered health care provider visits by 13% (RR 0.87; p=0.024)

The model estimated that vaccination of every 100 healthy, working adults with LAIV prevented 12.3 work day absenteeisms and 2.5 physician visits. The economic evaluation estimated a mean cost neutral point (cost for vaccine and administration equals cost of influenza cases prevented) was $43.07 (median $41.16; 5th-95th percentiles, $25.72 to $58.92)—1998 US dollars. The results of the cost-benefit analysis indicate that vaccinating healthy working adults would result in both substantial health and economic benefits.

Table 27.— Summary of FluMist® Pharmacoeconomic Studies

Publication & Related Protocol Number	Comparators	Subjects Age	Study Type	Study Perspective	Study Input Variables	Study Influenza Season(s)	Influenza Attack Rate (During Study Season)	Key Findings
Luce, 2008 (MI-CP111)	LAIV vs. TIV	24-59 months	CE/CU	Societal	Primary results from a 1-year, prospective, active-controlled, RCT efficacy trial (*Belshe 2007*); cost data captured via literature	2004-2005	N/A	• Estimated a cost savings of about $46 in LAIV cohort compared to TIV cohort • Cost savings remained throughout wide range of sensitivity analyses
Prosser, 2006	TIV (high & low risk) or LAIV (low risk) vs. Placebo	6 months – 17 years	CE/CU	Societal	Literature-based	N/A	6%-15.7%	• In low risk children, LAIV was estimated to have similar cost per event prevented than TIV, although point estimates were consistently lower in LAIV cohorts • In LAIV cohort, CU ranged from $15,000/QALY (2 year olds) to $109,000/QALY (12-17 year olds)
Luce, 2001 (AV006)	LAIV vs. Placebo	15-85 months	CE/ breakeven analysis	Societal, individual office setting and group-based setting	Primary results from a 2-year, prospective, placebo-controlled, RCT efficacy trial (*Belshe 1998, 2000*); cost data captured via literature	1996-1997 & 1997-1998	17.9%, culture confirmed (Placebo)	• At $20 per dose for vaccine and administration, the CE for LAIV was estimated at $30/febrile ILI day avoided (office setting) and cost saving in group setting • Estimated cost point where cost of disease equaled vaccination cost was about $5 (office) and about $28 (group)
Schmier, 2008 (SchoolMist)	LAIV School Vaccination Intervention vs. No Intervention	5-18 years	CC	Societal, Influenza peak week and projected influenza season	Primary results from a single-season, prospective, cluster-controlled intervention study (*King 2006*); cost data captured via literature	2004-2005	26%, symptoms – fever + cough or sore throat (Placebo)	• If examine peak influenza week only, school-located vaccination program with LAIV found to be cost neutral • If extrapolate across entire season, household savings was about $172
Hibbert, 2007 (D153—P502)	LAIV Daycare Vaccination Intervention vs. No Intervention	6-36 months	CE	Societal	Primary results from a 2-year, prospective, placebo-controlled, RCT efficacy trial (*Vesikari 2006*); cost data captured via literature	2001-2002 & 2002-2003	10.9%-30.4%, culture confirmed (Placebo)	• Study results from Season 1 were estimated to have about a $5 savings per vaccinated child • Season 2 was estimated to result in about a $144 savings per child vaccinated
Nichol, 2003 (AV009)	LAIV vs. Placebo	18-64 years, healthy employed adults	CB/ breakeven analysis	Societal	Primary results from a single-season prospective, placebo-controlled, RCT efficacy trial (*Nichol 1999*); cost data captured via literature	1997-1998	20.9%, symptoms – fever + URI (Placebo)	• Estimated cost point where cost of disease equaled vaccination cost was about $43

CB = cost benefit; CE = cost effectiveness; CU = cost utility; LAIV = live, attenuated influenza vaccine, trivalent (FluMist®); RCT = randomized control trial; TIV = inactivated influenza vaccine, trivalent; URI = upper respiratory illness.

VII. Formulation, Dosage, and Administration

FluMist® was licensed in the United States in 2003 as a frozen formulation. It was reformulated in the 2007-2008 season so that it may be stored at refrigerator temperatures (2˚-8˚C/35˚-46˚F), and this is the only formulation now currently available. In addition, the dose volume has been reduced by 60% compared with the previously available frozen FluMist® formulation (see Table 28 for details). As detailed earlier in Tables 7 and 8 (Chapter 3), both formulations have been studied in clinical development trials and thus appear in the published literature.

Potency

Each 0.2 mL dose of FluMist® is formulated to contain $10^{6.5-7.5}$ FFU (fluorescent focus units) for each of the 3 influenza virus strains recommended by the US Public Health Service (USPHS) for the current influenza season. FFU measurement replaces the earlier-used $TCID_{50}$ (tissue culture infectious doses) dose calibration for frozen FluMist® and offers several advantages in terms of assay speed, accuracy and precision. Overall, the target potency of FluMist® remains similar to past formulations.

The FluMist® package insert (product labeling) is updated annually to reflect the influenza virus strains included in the vaccine for the current season. FluMist® vaccine contains live attenuated virus that also expresses the core (internal) influenza virus proteins—a distinct product feature—and the same major surface antigens (hemagglutinin and neuraminidase) as the injectable trivalent inactivated influenza vaccine (TIV). However, TIV dose is expressed in terms of HA content (i.e., 15 mcg per viral strain) and cannot be equated to the potency expression for FluMist®. For a comparison by the CDC of TIV and FluMist® vaccines, see Table 29.

Table 28.— Formulation Comparison of Frozen FluMist® and Refrigerated FluMist®

Formulation Comparison		
Characteristic	**Frozen FluMist® (available only during 2003-2006 seasons)**	**Refrigerated FluMist® (currently available formulation)**
U.S. Licensure status	Licensed in 2003 for healthy individuals 5-49 years of age	Licensed in 2007 for individuals 2-49 years of age
Strains and valency	Trivalent LAIV	Trivalent LAIV
Concentration	$10^{6.5-7.5}$ $TCID_{50}$ (median tissue culture infectious dose) of each strain per dose	$10^{6.5-7.5}$ FFU (fluorescence focus units) of each strain per dose
Excipients (per dose)	Egg allantoic fluid (containing 190-470 mcg/mL of egg ovalbumin) . . . . . q.s. 0.5 mL Sucrose . . . . . 37.31 mg Dibasic potassium phosphate . . . . . 0.63 mg Monosodium phosphate . . . . . 0.26 mg Monosodium glutamate (MSG) . . . . . 0.47 mg Gentamicin sulfate . . . . . <0.015 mcg/mL	Stabilizing buffer fluid (containing ≤1.2 mcg/mL of egg ovalbumin) . . . . . q.s. 0.2 mL Sucrose . . . . . 13.68 mg Dibasic potassium phosphate . . . . . 2.26 mg Monosodium phosphate . . . . . 0.96 mg Monosodium glutamate . . . . . 0.19 mg Arginine (amino acid) . . . . . 2.42 mg Hydrolyzed porcine gelatin . . . . . 2.0 mg Gentamicin sulfate . . . . . <0.015 mcg/mL
Storage	Freezer: less than -15˚C (less than +5˚F)	Refrigerator: 2˚ to 8˚C (35˚-46˚F)
Room temperature stability (immediately prior to use)	1 hour	8 hours
Dosage	0.5 mL (0.25 mL per nostril)	0.2 mL (0.1 mL per nostril)

Table 29.— Live, Attenuated Influenza Vaccine (LAIV) Compared with Inactivated Influenza Vaccine (TIV) for Seasonal Influenza, United States Formulations (from CDC/ACIP 2008).

Factor	LAIV	TIV
Route of administration	Intranasal spray	Intramuscular injection
Type of vaccine	Live-attenuated virus	Killed virus
Number of included virus strains	3 (2 influenza A, 1 influenza B)	3 (2 influenza A, 1 influenza B)
Vaccine virus strains updated	Annually	Annually
Frequency of administration	Annually[a]	Annually[a]
Approved age	Persons aged 2-49 years[b]	Persons aged ≥6 months
Interval between 2 doses recommended for children aged ≥6 months–8 years who are receiving influenza vaccine for the first time	4 weeks	4 weeks
Can be administered to persons with medical risk factors for influenza-related complications[b]	No	Yes
Can be administered to children with asthma or children aged 2–4 years with wheezing during the preceding year[c]	No	Yes
Can be administered to family members or close contacts of immunosuppressed persons not requiring a protected environment	Yes	Yes
Can be administered to family members or close contacts of immunosuppressed persons requiring a protected environment (e.g., hematopoietic stem cell transplant recipient)	No	Yes
Can be administered to family members or close contacts of persons at high risk but not severely immunosuppressed	Yes	Yes
Can be simultaneously administered with other vaccines	Yes[d]	Yes[e]
If not simultaneously administered, can be administered within 4 weeks of another live vaccine	Prudent to space 4 weeks apart	Yes
If not simultaneously administered, can be administered within 4 weeks of an inactivated vaccine	Yes	Yes

[a] Children aged 6 months-8 years who have never received influenza vaccine before should receive 2 doses. Those who only receive 1 dose in their first year of vaccination should receive 2 doses in the following year, spaced 4 weeks apart.

[b] Persons at high risk for complications of influenza infection because of underlying medical conditions should not receive LAIV. Persons at higher risk for complications of influenza infection because of underlying medical conditions include adults and children with chronic disorders of the pulmonary or cardiovascular systems; adults and children with chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunnosuppression; children and adolescents receiving long-term aspirin therapy (at risk for developing Reye syndrome after wild-type influenza infection); persons who have any condition (e.g., cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration; pregnant women; and residents of nursing homes and other chronic-care facilities that house persons with chronic medical conditions.

[c] Clinicians and vaccination programs should screen for possible reactive airways diseases when considering use of LAIV for children aged 2-4 years, and should avoid use of this vaccine in children with asthma or a recent wheezing episode. Health-care providers should consult the medical record, when available, to identify children aged 2-4 years with asthma or recurrent wheezing that might indicate asthma. In addition, to identify children who might be at greater risk for asthma and possibly at increased risk for wheezing after receiving LAIV, parents or caregivers of children aged 2-4 years should be asked: "In the past 12 months, has a health-care provider ever told you that your child had wheezing or asthma?" Children whose parents or caregivers answer "yes" to this question and children who have asthma or who had a wheezing episode noted in the medical record during the preceding 12 months, should not receive FluMist®.

[d] Live attenuated influenza vaccine coadministration has been evaluated systematically only among children aged 12-15 months who received measles, mumps and rubella vaccine or varicella vaccine.

[e] Inactivated influenza vaccine coadministration has been evaluated systematically only among adults who received pneumococcal polysaccharide or zoster vaccine.

Please see accompanying Full Prescribing Information (Package Insert).

Excipients

FluMist® contains negligible amounts of gentamicin, and a small amount of soluble buffer (sucrose, phosphate, and glutamate) arginine and hydrolyzed porcine gelatin. FluMist® is completely free of thimerosal (preservative) and other mercury-containing salts. The most common protein excipient is from the gelatin that is used in the processing and titration of the final aqueous dosage form. As with all vaccines, **epinephrine injection (1:1000) or comparable treatment must be readily available in the event of an acute anaphylactic reaction following FluMist® vaccination**. The health care provider should ensure prevention of any allergic or other adverse reactions by reviewing the individual's history for possible sensitivity to influenza vaccine components, including eggs.

Spray Device

FluMist® is supplied as a single-use, pre-filled intranasal spray device in 10-sprayer packages (NDC # 66019-105-01). Each pre-filled FluMist® sprayer contains 0.2 mL dose volume (i.e., 0.1 mL for each nostril); a dose divider clip is removed from the plunger of the sprayer to administer the second half of the dose (see Figure 14). The plastic components of the sprayer are made of either polyethylene or polypropylene polymers that are believed not to leach chemicals, including bisphenols, in any significant amount (*Wikipedia 2008*).

The FluMist® spray device has a teflon tip with a 1-way valve that produces a large-particle aerosol that is deposited in the nose and nasopharynx. With a typical hand-squeezed actuation, over 70% of the FluMist® aerosol is within the optimal size range (20 to 100 microns) for deposition in the nasal passages. In one published study, the mass mean aerodynamic diameter (MMAD) was found to be 60 ± 2 microns (*Bryant 1999*). Some droplets may drip down from the nose, but the majority are cleared by mucocilliary flow into the oropharyngeal tract (with a 50% mean clearance time of 50 minutes); less than 1% of the droplets reach the lower airways (*Bryant 1999*).

After stored FluMist® is readied, the tip of the sprayer is inserted just inside the nose and the plunger is depressed to spray the first half of the dose. (Note: Administration of FluMist® does not require any special action on the part of the individual being vaccinated. FluMist® recipients can breathe normally during administration.) 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. In actual use, approximately half of the dose from a single FluMist® sprayer (0.1 mL) is administered into each nostril while the recipient is in an upright position. These steps are illustrated in the package insert, as shown in Figure 15. Placebo demonstrator sprayers and a training DVD video are available from MedImmune upon request.

Once FluMist® has been administered, the sprayer should be disposed of according to the standard procedures for medical waste.

Because health care workers will likely administer FluMist® doses for the patient, it is important that they become trained on proper administration technique (see Figure 16).

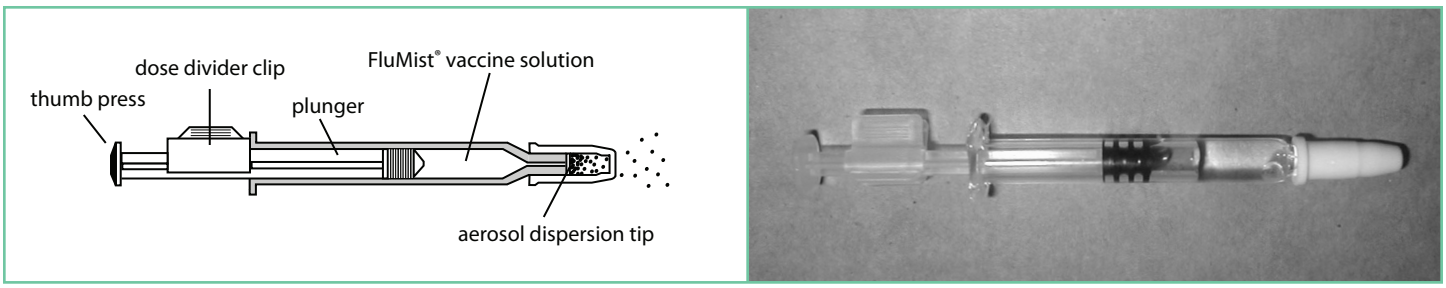

Figure 14.— FluMist® spray device.

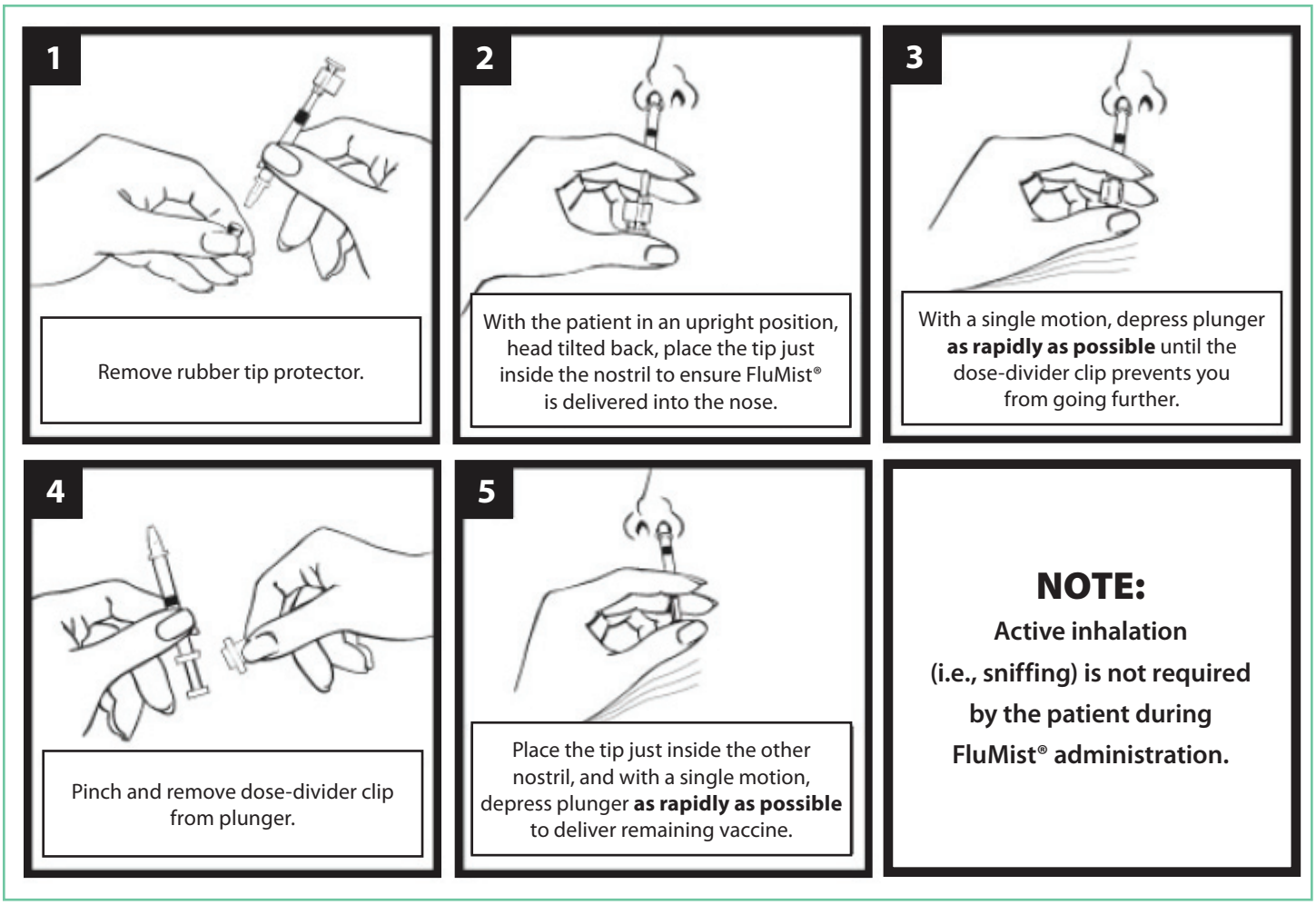

Figure 15.— FluMist® administration instructions.

Figure 16.— FluMist® (0.1 mL per nostril) being administered to a young child by a health care worker.

Biodistribution Pattern

The package insert notes that "*A biodistribution study of intranasally administered radiolabeled placebo was conducted in 7 healthy adult volunteers. The mean percentage of the delivered doses detected were as follows: nasal cavity 89.7%, stomach 2.6%, brain 2.4%, and lung 0.4%. The clinical significance of these findings is unknown.*"

In this study (protocol *PPL-338*) a tracer consisting of ^{99m}Tc-DTPA was added to the FluMist® vehicle placebo, and "delivered dose" was defined as all of the formulation that left the device and was deposited in the subjects. The majority of the initial dose (90%) was deposited in the nasal cavity area. Radioactivity detected in the areas of the cranium (2.4%) and lungs (0.4%) was attributed to scatter from the nasal cavity and stomach, respectively. Counts from the cranium region decreased over the 8-hour study period, with a clearance rate comparable to the nasal clearance curve, lending further support to the observed counts being scatter.

A second study (*protocol PPL-1014*) was conducted in 20 healthy adults to assess and compare the initial deposition patterns of frozen FluMist® and refrigerated FluMist® vehicle placebos in the nasal cavity and adjacent regions, including the cranium and lower respiratory tract, over a 4-hour period after dosing. The frozen FluMist® and refrigerated FluMist® placebo solutions contained the same radiolabelled tracer (^{99m}Tc-DTPA) as the earlier study. The majority of the refrigerated FluMist® placebo dose was delivered to the nasal cavity area (76.3%). The remaining portion of the dose was deposited variably in the areas of the nasopharynx (7.8%) and in the esophagus and stomach (4.2%). Very small percentages of radioactivity were found associated with the lung (0.9%) and cranium (2.5%) regions and were attributed to scatter. A greater deposition was observed in the oropharyngeal/stomach region for the frozen FluMist® placebo than the refrigerated FluMist® placebo, probably due to the larger volume of frozen FluMist® placebo, 0.5 mL, versus 0.2 mL for refrigerated FluMist® placebo.

Dose Schedule

The immunogenicity of influenza vaccines may be impacted by age, prior exposure to influenza viruses, and preexisting levels of immunity (*Keitel 1998*). In FluMist® clinical trials, a 2-dose schedule elicited the highest serum HA antibodies in a majority of immunologically näive young children (*Belshe 1998*, see Figure 10A and Table 11A in Chapter 3). For children 2 to 8 years of age who have not previously received influenza vaccine, the recommended dosage schedule is one 0.2 mL dose (given as 0.1 mL per nostril) followed by a second 0.2 mL dose given at least 4 weeks later. The CDC and AAP recommend that children aged 6 months to 8 years who received only 1 dose in their first year of vaccination receive 2 doses the following year (*CDC/ACIP 2008, AAP 2008*). For all other individuals, the recommended schedule is 1 dose (given as 0.1 mL per nostril).

FluMist® should be administered according to the dosage schedule shown in Table 30.

Vaccine and Drug/Lab Test Interactions

Presently there are limited clinical trial data for concurrent administration of FluMist® with other vaccines. (See Table 29 and below.) Clinical development studies of FluMist® excluded participants who received any live virus vaccine within 1 month prior to enrollment, and any inactivated or subunit vaccine within 2 weeks of enrollment.

Concurrent administration of FluMist® with live MMR (measles, mumps, and rubella) vaccine and/or varicella vaccine appeared safe and well tolerated in infants 12 to 15 months of age (*Nolan 2008*). Immune responses to the relevant viral antigens were similar when the vaccines were given concurrently or separately.

FluMist® should not be administered to persons on immunosuppressive therapy, including some of the new T-cell inhibitors for psoriasis, rheumatoid arthritis, or Crohn's disease (e.g., RAPTIVA®/efalizumab [Genentech], HUMIRA®/adalimumab [Abbott Labs],

Table 30.— FluMist® Dosage Schedule[a]

Age Group	Vaccination Status	Dosage Schedule
Children aged 2 years through 8 years	Not previously vaccinated with influenza vaccine	2 doses (0.2 mL each, at least 1 month apart)
Children aged 2 years through 8 years	Previously vaccinated with influenza vaccine[b]	1 dose (0.2 mL)
Children, adolescents, and adults aged 9 years through 49 years	Not applicable	1 dose (0.2 mL)

[a] A 0.2 mL dose is administered as 0.1 mL per nostril.
[b] Recommendation in prior seasons was that the previous dose had to be with FluMist® only.

Any refrigerator that reliably maintains a temperature of 2˚C-8˚C (35˚F-46˚F) is acceptable for storing FluMist®.

FluMist® is completely free of preservatives, including thimerosal or other mercury-containing salts.

and Cimzia®/certolizumab [UCB, Inc.], respectively. These products have a drug interaction label that lists all live vaccines.

FluMist® should not be administered until 48 hours after the cessation of antiviral therapy (e.g., neuraminidase inhibitors), and antiviral agents should not be administered until 2 weeks after administration of FluMist® unless medically indicated.

Children and adolescents receiving long-term aspirin therapy (at risk for developing Reye syndrome after wild-type influenza infection) should not receive FluMist®.

Intranasal corticosteroids are generally accepted as not causing immune suppression and have been used in children receiving FluMist® (*Piedra 2005*). No safety or efficacy issues were reported in these cases. There are no data regarding co-administration of FluMist® with other intranasal preparations.

Lab test interference is dependent on the length of time that FluMist® can be recovered from nasal specimens of children and adults. Nasopharyngeal secretions or swabs collected from vaccinees may test positive for influenza virus for up to 3 weeks following FluMist® administration. In a study of nasopharyngeal swab specimens from 14 healthy adults, 7 (50%) had a direct fluorescent antibody test (DFA) result and 2 (14%) had an enzyme immunoassay (EIA) result that was positive for influenza antigen within 7 days after FluMist® administration (*Ali 2004*). No subjects had positive results on day 12 or 13 after vaccination.

Please see accompanying Full Prescribing Information (Package Insert).

VIII. Storage and Handling

As a cold-adapted, temperature-sensitive, live (attenuated) virus vaccine, FluMist® requires maintenance of cold-chain conditions throughout its shipping and handling prior to use. FluMist® is manufactured and shipped to distributors as a frozen product. Thereafter and upon receipt by the health care provider, FluMist® should be stored in a refrigerator at 2˚C to 8˚C (35˚F to 46˚F). **Do not refreeze.** Inadvertent freezing for prolonged periods followed by repeated thawing can render the vaccine subpotent. The following is a review of the cold-chain conditions required for FluMist®.

Shipment, Receipt, and Storage

FluMist® is shipped by MedImmune to distributors under dry ice. (Note: Dry ice has a temperature of -78˚C [-108˚F] and must be handled carefully. Momentary skin contact with dry ice can cause frostbite and blisters.)

When the shipment arrives, distributors may store in a refrigerator until subsequent delivery is made to health care providers (e.g., pharmacies, clinics, medical offices). Distributors should ship the FluMist® vaccine under refrigerated conditions (2˚C-8˚C) to their customers.

When the health care provider receives a FluMist® shipment from their distributor, it should be inspected for temperature compliance. Immediately after, FluMist® sprayers should be placed into a properly maintained refrigerator (2˚C-8˚C).

Transportation

As noted in the package insert, the cold chain must be maintained when transporting FluMist® prior to use. FluMist® should remain at a temperature within the range of 2˚C to 8˚C (35˚F to 46˚F) until it is used. If it is desired or necessary to move FluMist® to another storage location, the packaged sprayers, in their original cartons, should be transported in a suitable portable device or insulated container capable of holding cold packs or ice to ensure the product remains refrigerated during transport.

Handling

FluMist® should never be placed in a microwave oven or any other heating equipment. If removed from refrigerator storage for patient administration and held at room temperature (25˚C/77˚F) beforehand, it should be used within 8 hours. Any unused vaccine left at room temperature for an appreciable time should be discarded, as its potency may be reduced.

There is no specific recommendation for wearing gloves when handling FluMist®; however, there may be a potential for breakage or spillage when holding FluMist® in the palm of the hand. Each health care worker should follow his or her institution's standard medical procedure regarding wearing gloves for the administration of live virus vaccines.

FluMist® is a colorless to pale yellow liquid and is clear to slightly cloudy; some proteinacious particulates may be present but do not affect the use of the product.

After removing the FluMist® vaccine from refrigerator storage for patient administration, at room temperature (25˚C/77˚F), it should be used within 8 hours.

FluMist® should not be used after the expiration date on the label.

The FluMist® sprayer should be disposed of as standard medical waste.

Disposal

The FluMist® sprayer should be disposed of as standard medical waste (e.g., in a red bag or sharps container). In case of accidental spillage, countertops may be cleaned with disinfectant solutions such as 0.25% sodium hypochlorite solution (bleach), ethyl or isopropyl alcohol 70-90%, or 0.5% phenol (Lysol®) (*AAP 2001*). Materials that are used to clean up FluMist® should also be disposed as standard medical waste.

Product Shelf Life

Information obtained from ongoing and completed drug product stability studies supports a shelf life of up to 18 weeks (after the date of issue to distributors). **FluMist® should not be used after the expiration date on the label.** (Note: The composition of FluMist® and other influenza vaccines changes each season to match the expected circulating strains of influenza virus.)

To discuss any additional questions about FluMist® stability, storage and handling, or product quality, or to request placebo demonstrator sprayers, call 1-877-FLUMIST. For other medical information regarding FluMist®, please call 1-800-949-3789 or 1-877-633-4411.

Pricing Information

FluMist® pricing to health care professionals for the 2008-2009 influenza season will be $18.95 per dose + $.75 per dose federal excise tax.

A FluMist® customer service representative will be available **8:30 AM to 5:30 PM EST at 1-877-FLUMIST** to help address any questions or concerns.

Please see accompanying Full Prescribing Information (Package Insert).

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FluMist safely and effectively. See full prescribing information for FluMist.

FluMist® Influenza Virus Vaccine Live, Intranasal
Intranasal Spray
2008-2009 Formula
Initial U.S. Approval: 2003

RECENT MAJOR CHANGES

Indications and Usage (1)	9/2007
Dosage and Administration, Dosing Information (2.1)	9/2007
Warnings and Precautions (5)	9/2007

INDICATIONS AND USAGE

FluMist is a vaccine indicated for the active immunization of individuals 2-49 years of age against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. (1)

DOSAGE AND ADMINISTRATION

For intranasal administration by a health care provider.

Age Group	Vaccination Status	Dosage Schedule
Children (2-8 years)	Not previously vaccinated with influenza vaccine	2 doses (0.2 mL* each, at least 1 month apart) (2.1)
Children (2-8 years)	Previously vaccinated with influenza vaccine	1 dose (0.2 mL*) (2.1)
Children, adolescents and adults (9-49 years)	Not applicable	1 dose (0.2 mL*) (2.1)

* Administer as 0.1 mL per nostril.

DOSAGE FORMS AND STRENGTHS

0.2 mL pre-filled, single-use intranasal spray (3)
Each 0.2 mL dose contains $10^{6.5-7.5}$ FFU (fluorescent focus units) of live attenuated influenza virus reassortants of each of the three strains for the 2008-2009 season: A/South Dakota/6/2007 (H1N1) (A/Brisbane/59/2007-like), A/Uruguay/716/2007 (H3N2) (A/Brisbane/10/2007-like), and B/Florida/4/2006. (3)

CONTRAINDICATIONS

- Hypersensitivity to eggs, egg proteins, gentamicin, gelatin or arginine or life threatening reactions to previous influenza vaccination. (4.1)
- Concomitant aspirin therapy in children and adolescents. (4.2)

WARNINGS AND PRECAUTIONS

- Do not administer FluMist to children <24 months of age because of increased risk of hospitalization and wheezing observed in clinical trials. (5.1)
- FluMist should not be administered to any individuals with asthma or children < 5 years of age with recurrent wheezing because of the potential for increased risk of wheezing post vaccination. (5.2)
- If Guillain-Barré syndrome has occurred with any prior influenza vaccination, the decision to give FluMist should be based on careful consideration of the potential benefits and risks. (5.3)
- Administration of FluMist, a live virus vaccine, to immunocompromised persons should be based on careful consideration of potential benefits and risks. (5.4)
- Safety has not been established in individuals with underlying medical conditions predisposing them to wild-type influenza infection complications. (5.5)

ADVERSE REACTIONS

Most common adverse reactions (≥ 10% in FluMist and at least 5% greater than in control) are runny nose or nasal congestion in all ages, fever >100°F in children 2-6 years of age, and sore throat in adults. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact MedImmune at 1-877-633-4411 or VAERS at 1-800-822-7967 or *http://vaers.hhs.gov.*

DRUG INTERACTIONS

- Antiviral agents active against influenza A and/or B: Do not administer FluMist until 48 hours after antiviral cessation. Antiviral agents should not be administered until 2 weeks after FluMist administration unless medically necessary. (7.2)

USE IN SPECIFIC POPULATIONS

- Safety and effectiveness of FluMist have not been studied in pregnant women or nursing mothers. (8.1, 8.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 06/2008

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FluMist is a vaccine indicated for the active immunization of individuals 2-49 years of age against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine.

2 DOSAGE AND ADMINISTRATION

FOR INTRANASAL ADMINISTRATION BY A HEALTH CARE PROVIDER.

2.1 Dosing Information

FluMist should be administered according to the following schedule:

Age Group	Vaccination Status	Dosage Schedule
Children age 2 years through 8 years	Not previously vaccinated with influenza vaccine	2 doses (0.2 mL* each, at least 1 month apart)
Children age 2 years through 8 years	Previously vaccinated with influenza vaccine	1 dose (0.2 mL*)
Children, adolescents and adults age 9 through 49 years	Not applicable	1 dose (0.2 mL*)

* Administer as 0.1 mL per nostril.

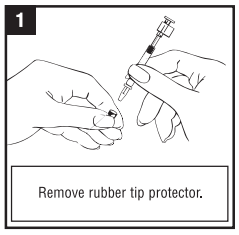
For children age 2 years through 8 years who have not previously received influenza vaccine, the recommended dosage schedule for nasal administration is one 0.2 mL dose (0.1 mL per nostril) followed by a second 0.2 mL dose (0.1 mL per nostril) given at least 1 month later.

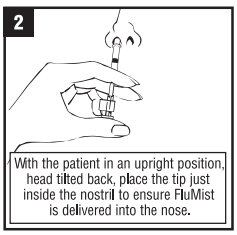
For all other individuals, including children age 2-8 years who have previously received influenza vaccine, the recommended schedule is one 0.2 mL dose (0.1 mL per nostril).

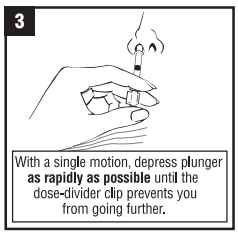
FluMist should be administered prior to exposure to influenza. Annual revaccination with influenza vaccine is recommended.

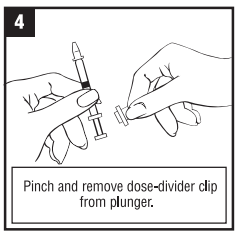
2.2 Administration Instructions

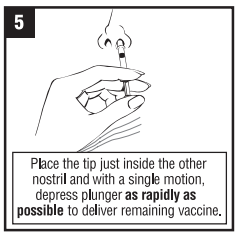
Each sprayer contains a single dose of FluMist; approximately one-half of the contents should be administered into each nostril. 0.1 mL (i.e., half of the dose from a single FluMist sprayer) is administered into each nostril while the recipient is in an upright position. Insert the tip of the sprayer just inside the nose and rapidly depress the plunger until the dose-divider clip stops the plunger. The dose-divider clip is removed from the sprayer to administer the second half of the dose (0.1 mL) into the other nostril. Once FluMist has been administered, the sprayer should be disposed of according to the standard procedures for medical waste (e.g., sharps container or biohazard container).











Note:
Active inhalation (i.e., sniffing) is not required by the patient during FluMist administration.

3 DOSAGE FORMS AND STRENGTHS

0.2 mL pre-filled, single-use intranasal spray.

Each 0.2 mL dose of FluMist is formulated to contain $10^{6.5\text{-}7.5}$ FFU (fluorescent focus units) of each of three live attenuated influenza virus reassortants: A/South Dakota/6/2007 (H1N1) (A/Brisbane/59/2007-like), A/Uruguay/716/2007 (H3N2) (A/Brisbane/10/2007-like), and B/Florida/4/2006 [1].

4 CONTRAINDICATIONS

4.1 Hypersensitivity

FluMist is contraindicated in individuals with a history of hypersensitivity, especially anaphylactic reactions, to eggs, egg proteins, gentamicin, gelatin, or arginine or with life-threatening reactions to previous influenza vaccinations.

4.2 Concomitant Pediatric and Adolescent Aspirin Therapy and Reye's Syndrome

FluMist is contraindicated in children and adolescents (2-17 years of age) receiving aspirin therapy or aspirin-containing therapy, because of the association of Reye's syndrome with aspirin and wild-type influenza infection.

5 WARNINGS AND PRECAUTIONS

5.1 Risks in Children <24 Months of Age

Do not administer FluMist to children <24 months of age. In clinical trials, an increased risk of wheezing post-vaccination was observed in FluMist recipients <24 months of age. An increase in hospitalizations was observed in children <24 months of age after vaccination with FluMist. [*See Adverse Reactions (6.1)*.]

5.2 Asthma/Recurrent Wheezing

FluMist should not be administered to any individuals with asthma or children <5 years of age with recurrent wheezing because of the potential for increased risk of wheezing post vaccination unless the potential benefit outweighs the potential risk.

Do not administer FluMist to individuals with severe asthma or active wheezing because these individuals have not been studied in clinical trials.

5.3 Guillain-Barré Syndrome

If Guillain-Barré syndrome has occurred within 6 weeks of any prior influenza vaccination, the decision to give FluMist should be based on careful consideration of the potential benefits and potential risks [*see also Adverse Reactions (6.2)]*.

5.4 Altered Immunocompetence

Administration of FluMist, a live virus vaccine, to immunocompromised persons should be based on careful consideration of potential benefits and risks. Although FluMist was studied in 57 asymptomatic or mildly symptomatic adults with HIV infection *[see Clinical Studies (14.3)],* data supporting the safety and effectiveness of FluMist administration in immunocompromised individuals are limited.

5.5 Medical Conditions Predisposing to Influenza Complications

The safety of FluMist in individuals with underlying medical conditions that may predispose them to complications following wild-type influenza infection has not been established. FluMist should not be administered unless the potential benefit outweighs the potential risk.

5.6 Management of Acute Allergic Reactions

Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of the vaccine *[see Contraindications (4.1)]*.

5.7 Limitations of Vaccine Effectiveness

FluMist may not protect all individuals receiving the vaccine.

6 ADVERSE REACTIONS

FluMist is not indicated in children <24 months of age. In a clinical trial, among children 6-23 months of age, wheezing requiring bronchodilator therapy or with significant respiratory symptoms occurred in 5.9% of FluMist recipients compared to 3.8% of active control (injectable influenza vaccine made by Sanofi Pasteur Inc.) recipients (Relative Risk 1.5, 95% CI: 1.2, 2.1). Wheezing was not increased in children ≥24 months of age.

Hypersensitivity, including anaphylactic reaction, has been reported post-marketing.

[See *Warnings and Precautions (5.1)* and *Adverse Reactions (6.1, 6.2)*.]

6.1 Adverse Reactions in Clinical Trials

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 9537 children and adolescents 1-17 years of age and 3041 adults 18-64 years of age received FluMist in randomized, placebo-controlled Studies D153-P501, AV006, D153-P526, AV019 and AV009 described below. In addition, 4179 children 6-59 months of age received FluMist in Study MI-CP111, a randomized, active-controlled trial. Among pediatric FluMist recipients 6 months-17 years of age, 50% were female; in the study of adults, 55% were female. In MI-CP111, AV006, D153-P526, AV019 and AV009, subjects were White (71%), Hispanic (11%), Asian (7%), Black (6%), and Other (5%), while in D153-P501, 99% of subjects were Asian.

Adverse Reactions in Children and Adolescents

In a placebo-controlled safety study (AV019) conducted in a large Health Maintenance Organization (HMO) in children 1-17 years of age (n = 9689), an increase in asthma events, captured by review of diagnostic codes, was observed in children <5 years of age (Relative Risk 3.53, 90% CI: 1.1, 15.7). This observation was prospectively evaluated in Study MI-CP111.

In MI-CP111, an active-controlled study, increases in wheezing and hospitalization (for any cause) were observed in children <24 months of age, as shown in Table 1.

Table 1
Percentages of Children with Hospitalizations and Wheezing from MI-CP111

Adverse Reaction	Age Group	FluMist	Active Control[a]
Hospitalizations[b]	6-23 months (n = 3967)	4.2 %	3.2 %
	24-59 months (n= 4385)	2.1 %	2.5 %
Wheezing[c]	6-23 months (n = 3967)	5.9 %	3.8 %
	24-59 months (n = 4385)	2.1 %	2.5 %

[a] Injectable influenza vaccine made by Sanofi Pasteur Inc.
[b] From randomization through 180 days post last vaccination.
[c] Wheezing requiring bronchodilator therapy or with significant respiratory symptoms evaluated from randomization through 42 days post last vaccination.

Most hospitalizations observed were gastrointestinal and respiratory tract infections and occurred more than 6 weeks post vaccination. In post hoc analysis, rates of hospitalization in children 6-11 months of age (n = 1376) were 6.1% in FluMist recipients and 2.6% in active control recipients.

Table 2 shows an analysis of pooled solicited events, occurring in at least 1% of FluMist recipients and at a higher rate compared to placebo, post Dose 1 for Study D153-P501 and AV006 and solicited events post Dose 1 for Study MI-CP111. Solicited events were those about which parents/guardians were specifically queried after vaccination with FluMist. In these studies, solicited events were documented for 10 days post vaccination. Solicited events post Dose 2 for FluMist were similar to those post Dose 1 and were generally observed at a lower frequency.

Table 2
Summary of Solicited Events Observed within 10 Days after Dose 1 for Vaccine[a] and either Placebo or Active Control Recipients; Children 2-6 Years of Age

	D153-P501 & AV006		MI-CP111	
	FluMist N=876-1759[c]	Placebo N=424-1034[c]	FluMist N=2170[c]	Active Control[b] N=2165[c]
Event	%	%	%	%
Runny Nose/ Nasal Congestion	58	50	51	42
Decreased Appetite	21	17	13	12
Irritability	21	19	12	11
Decreased Activity (Lethargy)	14	11	7	6
Sore Throat	11	9	5	6
Headache	9	7	3	3
Muscle Aches	6	3	2	2
Chills	4	3	2	2
Fever				
100-101°F Oral	9	6	6	4
101-102°F Oral	4	3	4	3

[a] Frozen formulation used in AV006; Refrigerated formulation used in D153-P501 and MI-CP111.
[b] Injectable influenza vaccine made by Sanofi Pasteur Inc.
[c] Number of evaluable subjects (those who returned diary cards) for each event. Range reflects differences in data collection between the 2 pooled studies.

In clinical studies D153-P501 and AV006, other adverse reactions in children occurring in at least 1% of FluMist recipients and at a higher rate compared to placebo were: abdominal pain (2% FluMist vs. 0% placebo) and otitis media (3% FluMist vs. 1% placebo).

An additional adverse reaction identified in the active-controlled trial, MI-CP111, occurring in at least 1% of FluMist recipients and at a higher rate compared to active control was sneezing (2% FluMist vs. 1% active control).

In a separate trial (MI-CP112) that compared the refrigerated and frozen formulations of FluMist in children and adults 5-49 years of age, the solicited events and other adverse events were consistent with observations from previous trials. Fever of >103°F was observed in 1 to 2% of children 5-8 years of age.

In a separate placebo-controlled trial (D153-P526) using the refrigerated formulation in a subset of older children and adolescents 9-17 years of age who received one dose of FluMist, the solicited events and other adverse events were generally consistent with observations from previous trials. Abdominal pain was reported in 12% of FluMist recipients compared to 4% of placebo recipients and decreased activity was reported in 6% of FluMist recipients compared to 0% of placebo recipients.

Adverse Reactions in Adults

In adults 18-49 years of age in Study AV009, summary of solicited adverse events occurring in at least 1% of FluMist recipients and at a higher rate compared to placebo include runny nose (44% FluMist vs. 27% placebo), headache (40% FluMist vs. 38% placebo), sore throat (28% FluMist vs. 17% placebo), tiredness/weakness (26% FluMist vs. 22% placebo), muscle aches (17% FluMist vs. 15% placebo), cough (14% FluMist vs. 11% placebo), and chills (9% FluMist vs. 6% placebo).

In addition to the solicited events, other adverse reactions from Study AV009 occurring in at least 1% of FluMist recipients and at a higher rate compared to placebo were: nasal congestion (9% FluMist vs. 2% placebo) and sinusitis (4% FluMist vs. 2% placebo).

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of FluMist. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to vaccine exposure.

Congenital, familial and genetic disorder: Exacerbation of symptoms of mitochondrial encephalomyopathy (Leigh syndrome).

Gastrointestinal disorders: Nausea, vomiting, diarrhea

Immune system disorders: Hypersensitivity reactions (including anaphylactic reaction, facial edema and urticaria)

Nervous system disorders: Guillain-Barré syndrome, Bell's Palsy

Respiratory, thoracic and mediastinal disorders: Epistaxis

Skin and subcutaneous tissue disorders: Rash

7 DRUG INTERACTIONS

7.1 Aspirin Therapy

Do not administer FluMist to children or adolescents who are receiving aspirin therapy or aspirin-containing therapy *[see Contraindications (4.2)]*.

7.2 Antiviral Agents Against Influenza A and/or B

The concurrent use of FluMist with antiviral agents that are active against influenza A and/or B viruses has not been evaluated. However, based upon the potential for antiviral agents to reduce the effectiveness of FluMist, do not administer FluMist until 48 hours after the cessation of antiviral therapy and antiviral agents should not be administered until two weeks after administration of FluMist unless medically indicated. If antiviral agents and FluMist are administered concomitantly, revaccination should be considered when appropriate.

7.3 Concomitant Inactivated Vaccines

The safety and immunogenicity of FluMist when administered concurrently with inactivated vaccines have not been determined. Studies of FluMist excluded subjects who received any inactivated or subunit vaccine within two weeks of enrollment. Therefore, healthcare providers should consider the risks and benefits of concurrent administration of FluMist with inactivated vaccines.

7.4 Concomitant Live Vaccines

Concurrent administration of FluMist with the measles, mumps and rubella vaccine and the varicella vaccine was studied in 1245 children 12-15 months of age. Adverse events were similar to those seen in other clinical trials with FluMist *[see Adverse Reactions (6.1)]*. No evidence of interference with immune responses to measles, mumps, rubella, varicella and FluMist vaccines was observed. The safety and immunogenicity in children >15 months of age have not been studied.

7.5 Intranasal Products

There are no data regarding co-administration of FluMist with other intranasal preparations.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with FluMist. It is not known whether FluMist can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. FluMist should be given to a pregnant woman only if clearly needed.

The effect of the vaccine on embryo-fetal and pre-weaning development was evaluated in a developmental toxicity study using pregnant rats receiving the frozen formulation. Groups of animals were administered the vaccine either once (during the period of organogenesis on gestation day 6) or twice (prior to gestation and during the period of organogenesis on gestation day 6), 250 microliter/rat/occasion (approximately 110-140 human dose equivalents), by intranasal instillation. No adverse effects on pregnancy, parturition, lactation, embryo-fetal or pre-weaning development were observed. There were no vaccine related fetal malformations or other evidence of teratogenesis noted in this study.

8.3 Nursing Mothers

It is not known whether FluMist is excreted in human milk. Therefore, as some viruses are excreted in human milk and additionally, because of the possibility of shedding of vaccine virus and the close proximity of a nursing infant and mother, caution should be exercised if FluMist is administered to nursing mothers.

8.4 Pediatric Use

Safety and effectiveness of the vaccine has been demonstrated for children 2 years of age and older with reduction in culture-confirmed influenza rates compared to active control (injectable influenza vaccine made by Sanofi Pasteur Inc.) and placebo *[see Clinical Studies (14.1)]*. FluMist is not indicated for use in children <24 months of age. FluMist use in children <24 months has been associated with increased risk of hospitalization and wheezing in clinical trials *[see Warnings and Precautions (5.1)* and *Adverse Reactions (6.1)]*.

8.5 Geriatric Use

FluMist is not indicated for use in individuals ≥65 years of age. Subjects with underlying high-risk medical conditions (n=200) were studied for safety. Compared to controls, FluMist recipients had a higher rate of sore throat.

8.6 Use in Individuals 50-64 Years of Age

FluMist is not indicated for use in individuals 50-64 years of age. In Study AV009, effectiveness was not demonstrated in individuals 50-64 years of age (n=641). Solicited adverse events were similar in type and frequency to those reported in younger adults.

11 DESCRIPTION

FluMist (Influenza Virus Vaccine Live, Intranasal) is a live trivalent vaccine for administration by intranasal spray. The influenza virus strains in FluMist are (a) *cold-adapted* (*ca*) (i.e., they replicate efficiently at 25°C, a temperature that is restrictive for replication of many wild-type influenza viruses); (b) *temperature-sensitive (ts)* (i.e., they are restricted in replication at 37°C (Type B strains) or 39°C (Type A strains), temperatures at which many wild-type influenza viruses grow efficiently); and (c) *attenuated (att)* (they do not produce classic influenza-like illness in the ferret model of human influenza infection). The cumulative effect of the antigenic properties and the *ca*, *ts*, and *att* phenotypes is that the attenuated vaccine viruses replicate in the nasopharynx to induce protective immunity.

No evidence of reversion has been observed in the recovered vaccine strains that have been tested (135 of possible 250 recovered isolates) *[see Clinical Studies (14.5)]*. For each of the three reassortant strains in FluMist, the six internal gene segments responsible for *ca, ts*, and *att* phenotypes are derived from a master donor virus (MDV), and the two segments that encode the two surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA), are derived from the corresponding antigenically relevant wild-type influenza viruses that have been recommended by the USPHS for inclusion in the annual vaccine formulation. Thus, the three viruses contained in FluMist maintain the replication characteristics and phenotypic properties of the MDV and express the HA and NA of wild-type viruses that are related to strains expected to circulate during the 2008-2009 influenza season. For the Type A MDV, at least five genetic loci in three different internal gene segments contribute to the *ts* and *att* phenotypes. For the Type B MDV, at least three genetic loci in two different internal gene segments contribute to both the *ts* and *att* properties; five genetic loci in three gene segments control the *ca* property.

Specific pathogen-free (SPF) eggs are inoculated with each of the reassortant strains and incubated to allow vaccine virus replication. The allantoic fluid of these eggs is harvested, pooled and then clarified by filtration. The virus is concentrated by ultracentrifugation and diluted with stabilizing buffer to obtain the final sucrose and potassium phosphate concentrations. Ethylene diamine tetracetic acid (EDTA) is added to the dilution buffer for H3N2 strains. The viral harvests are then sterile filtered to produce the monovalent bulks. Each lot is tested for *ca*, *ts*, and *att* phenotypes and is also tested extensively by *in vitro* and *in vivo* methods to detect adventitious agents. Monovalent bulks from the three strains are subsequently blended and diluted as required to attain the desired potency with stabilizing buffers to produce the trivalent bulk vaccine. The bulk vaccine is then filled directly into individual sprayers for nasal administration.

Each pre-filled refrigerated FluMist sprayer contains a single 0.2 mL dose. Each 0.2 mL dose contains $10^{6.5\text{-}7.5}$ FFU of live attenuated influenza virus reassortants of each of the three strains: A/South Dakota/6/2007 (H1N1) (A/Brisbane/59/2007-like), A/Uruguay/716/2007 (H3N2) (A/Brisbane/10/2007-like), and B/Florida/4/2006 [1]. Each 0.2 mL dose also contains 0.188 mg/dose monosodium glutamate, 2.00 mg/dose hydrolyzed porcine gelatin, 2.42 mg/dose arginine, 13.68 mg/dose sucrose, 2.26 mg/dose dibasic potassium phosphate, 0.96 mg/dose monosodium phosphate, and <0.015 mcg/mL gentamicin sulfate. FluMist contains no preservatives.

The tip attached to the sprayer is equipped with a nozzle that produces a fine mist that is primarily deposited in the nose and nasopharynx. FluMist is a colorless to pale yellow liquid and is clear to slightly cloudy.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Immune mechanisms conferring protection against influenza following receipt of FluMist vaccine are not fully understood. Likewise, naturally acquired immunity to wild-type influenza has not been completely elucidated. Serum antibodies, mucosal antibodies and influenza-specific T cells may play a role in prevention and recovery from infection.

Influenza illness and its complications follow infection with influenza viruses. Global surveillance of influenza identifies yearly antigenic variants. For example, since 1977, antigenic variants of influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation. Antibody against one influenza virus type or subtype confers limited or no protection against another. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent development of antigenic variants through antigenic drift is the virologic basis for seasonal epidemics and the reason for the usual change of one or more new strains in each year's influenza vaccine. Therefore, influenza vaccines are standardized to contain the strains (i.e., typically two type A and one type B), representing the influenza viruses likely to be circulating in the United States in the upcoming winter.

Annual revaccination with the current vaccine is recommended because immunity declines during the year after vaccination, and because circulating strains of influenza virus change from year to year.

12.2 Biodistribution

A biodistribution study of intranasally administered radiolabeled placebo was conducted in 7 healthy adult volunteers. The mean percentage of the delivered doses detected were as follows: nasal cavity 89.7%, stomach 2.6%, brain 2.4%, and lung 0.4%. The clinical significance of these findings is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

FluMist has not been evaluated for its carcinogenic or mutagenic potential or its potential to impair fertility.

14 CLINICAL STUDIES

FluMist, in refrigerated and frozen formulations, was administered to approximately 35,000 subjects in controlled clinical studies. FluMist has been studied in placebo-controlled trials over multiple years, using different vaccine strains. Comparative efficacy has been studied where FluMist was compared to an inactivated influenza vaccine made by Sanofi Pasteur Inc.

14.1 Studies in Children and Adolescents

Study MI-CP111: Pediatric Comparative Study

A multinational, randomized, double-blind, active-controlled trial (MI-CP111) was performed to assess the efficacy and safety of FluMist compared to an injectable influenza vaccine made by Sanofi Pasteur Inc. (active control) in children <5 years of age, using the refrigerated formulation. During the 2004-2005 influenza season, a total number of 3916 children <5 years of age and without severe asthma, without use of bronchodilator or steroids and without wheezing within the prior 6 weeks were randomized to FluMist and 3936 were randomized to active control. Participants were then followed through the influenza season to identify illness caused by influenza virus. As the primary endpoint, culture-confirmed modified CDC-ILI (CDC-defined influenza-like illness) was defined as a positive culture for a wild-type influenza virus associated within ±7 days of modified CDC-ILI. Modified CDC-ILI was defined as fever (temperature ≥100°F oral or equivalent) plus cough, sore throat, or runny nose/nasal congestion on the same or consecutive days.

In the primary efficacy analysis, FluMist demonstrated a 44.5% (95% CI: 22.4, 60.6) reduction in influenza rate compared to active control as measured by culture-confirmed modified CDC-ILI caused by wild-type strains antigenically similar to those contained in the vaccine. See Table 3 for a description of the results by strain and antigenic similarity.

Table 3
Comparative Efficacy against Culture-Confirmed Modified CDC-ILI[a] Caused by Wild-Type Strains in Children <5 Years of Age

	FluMist			Active Control[b]			% Reduction in Rate for FluMist[c]	95% CI
	N	# of Cases	Rate (cases/N)	N	# of Cases	Rate (cases/N)		
Matched Strains								
All strains	3916	53	1.4%	3936	93	2.4%	44.5%	22.4, 60.6
A/H1N1	3916	3	0.1%	3936	27	0.7%	89.2%	67.7, 97.4
A/H3N2	3916	0	0.0%	3936	0	0.0%	—	—
B	3916	50	1.3%	3936	67	1.7%	27.3%	-4.8, 49.9
Mismatched Strains								
All strains	3916	102	2.6%	3936	245	6.2%	58.2%	47.4, 67.0
A/H1N1	3916	0	0.0%	3936	0	0.0%	—	—
A/H3N2	3916	37	0.9%	3936	178	4.5%	79.2%	70.6, 85.7
B	3916	66	1.7%	3936	71	1.8%	6.3%	-31.6, 33.3
Regardless of Match								
All strains	3916	153	3.9%	3936	338	8.6%	54.9%	45.4, 62.9
A/H1N1	3916	3	0.1%	3936	27	0.7%	89.2%	67.7, 97.4
A/H3N2	3916	37	0.9%	3936	178	4.5%	79.2%	70.6, 85.7
B	3916	115	2.9%	3936	136	3.5%	16.1%	-7.7, 34.7

ATP Population.

[a] Modified CDC-ILI was defined as fever (temperature ≥100°F oral or equivalent) plus cough, sore throat, or runny nose/nasal congestion on the same or consecutive days.

[b] Injectable influenza vaccine made by Sanofi Pasteur Inc.

[c] Reduction in rate was adjusted for country, age, prior influenza vaccination status, and wheezing history status.

Study D153-P501: Pediatric Study

A randomized, double-blind, placebo-controlled trial (D153-P501) was performed to evaluate the efficacy of FluMist in children 12 to 35 months of age without high-risk medical conditions against culture-confirmed influenza illness, using the refrigerated formulation. A total of 3174 children were randomized 3:2 (vaccine:placebo) to receive 2 doses of study vaccine or placebo at least 28 days apart in Year 1. See Table 4 for a description of the results.

Study AV006: Pediatric Study

AV006 was a multi-center, randomized, double-blind, placebo-controlled trial performed in U.S. children without high-risk medical conditions to evaluate the efficacy of FluMist against culture-confirmed influenza over two successive seasons using the frozen formulation. The primary endpoint of the trial was the prevention of culture-confirmed influenza illness due to antigenically matched wild-type influenza in children, who received two doses of vaccine in the first year and a single revaccination dose in the second year. During the first year of the study 1602 children 15-71 months of age were randomized 2:1 (vaccine:placebo). Approximately 85% of the participants in the first year returned for the second year of the study. In Year 2, children remained in the same treatment group as in year one and received a single dose of FluMist or placebo. See Table 4 for a description of the results.

Table 4
D153-P501 & AV006, Years 1[a]: Efficacy of FluMist vs. Placebo against Culture-Confirmed Influenza Illness due to Wild-Type Strains

	D153-P501			AV006		
	FluMist n[b] (%)	Placebo n[b] (%)	% Efficacy (95% CI)	FluMist n[b] (%)	Placebo n[b] (%)	% Efficacy (95% CI)
	N[c]=1653	N[c]=1111		N[c]=849	N[c]=410	
Any strain	56 (3.4%)	139 (12.5%)	72.9%[d] (62.8, 80.5)	10 (1%)	73 (18%)	93.4% (87.5, 96.5)
A/H1N1	23 (1.4%)	81 (7.3%)	80.9% (69.4, 88.5)[e]	0	0	—
A/H3N2	4 (0.2%)	27 (2.4%)	90.0% (71.4, 97.5)	4 (0.5%)	48 (12%)	96.0% (89.4, 98.5)
B	29 (1.8%)	35 (3.2%)	44.3% (6.2, 67.2)	6 (0.7%)	31 (7%)	90.5% (78.0, 95.9)

[a] D153-P501 and AV006 data are for subjects who received two doses of study vaccine.
[b] Number and percent of subjects in per-protocol efficacy analysis population with culture-confirmed influenza illness.
[c] Number of subjects in per-protocol efficacy analysis population of each treatment group of each study for the "any strain" analysis.
[d] For D153-P501, influenza circulated through 12 months following vaccination.
[e] Estimate includes A/H1N1 and A/H1N2 strains. Both were considered antigenically similar to the vaccine.

During the second year of Study AV006, the primary circulating strain was the A/Sydney/05/97 H3N2 strain, which was antigenically dissimilar from the H3N2 strain represented in the vaccine, A/Wuhan/359/95; FluMist demonstrated 87.0% (95% CI: 77.0, 92.6) efficacy against culture-confirmed influenza illness.

14.2 Study in Adults

AV009 was a multi-center, randomized, double-blind, placebo-controlled trial to evaluate effectiveness in adults 18-64 years of age without high-risk medical conditions. Participants were randomized 2:1, vaccine:placebo. Cultures for influenza virus were not obtained from subjects in the trial, so that the efficacy against culture-confirmed influenza was not assessed. The A/Wuhan/359/95 (H3N2) strain, which was contained in FluMist, was antigenically distinct from the predominant circulating strain of influenza virus during the trial period, A/Sydney/05/97 (H3N2). Type A/Wuhan (H3N2) and Type B strains also circulated in the U.S. during the study period. The primary endpoint of the trial was the reduction in the proportion of participants with one or more episodes of any febrile illness and prospective secondary endpoints were severe febrile illness, and febrile upper respiratory illness. Effectiveness for any of the three endpoints was not demonstrated in a subgroup of adults 50-64 years of age. Primary and secondary effectiveness endpoints from the age group 18-49 years of age are presented in Table 5. Effectiveness was not demonstrated for the primary endpoint in adults 18-49 years of age.

Table 5
Effectiveness of FluMist[a] in Adults 18–49 Years of Age During the 7-week Site-Specific Outbreak Period

Endpoint	FluMist N=2411[b] n (%)	Placebo N=1226[b] n (%)	Percent Reduction	(95% CI)
Participants with one or more events of:[c]				
Primary Endpoint:				
Any febrile illness	331 (13.73)	189 (15.42)	**10.9**	(-5.1, 24.4)
Secondary Endpoints:				
Severe febrile illness	250 (10.37)	158 (12.89)	**19.5**	(3.0, 33.2)
Febrile upper respiratory illness	213 (8.83)	142 (11.58)	**23.7**	(6.7, 37.5)

[a] Frozen formulation used.
[b] Number of evaluable subjects (92.7% and 93.0% of FluMist and placebo recipients, respectively).
[c] The predominantly circulating virus during the trial period was A/Sydney/05/97 (H3N2), an antigenic variant not included in the vaccine.

Effectiveness was shown in a post-hoc analysis using CDC-ILI in the age group 18-49 years.

14.3 Study in Adults with Human Immunodeficiency Virus (HIV) Infection

Safety and shedding of vaccine virus following FluMist administration were evaluated in 57 HIV-infected [median CD4 cell count of 541 cells/mm^3] and 54 HIV-negative adults 18-58 years of age in a randomized, double-blind, placebo controlled trial using the frozen formulation. No serious adverse events were reported during the one-month follow-up period. Vaccine strain (type B) virus was detected in 1 of 28 HIV-infected subjects on Day 5 only and none of the HIV-negative FluMist recipients. No adverse effects on HIV viral load or CD4 counts were identified following FluMist. The effectiveness of FluMist in preventing influenza illness in HIV-infected individuals has not been evaluated.

14.4 Refrigerated Formulation Study

A double-blind, randomized multi-center trial was conducted to evaluate the comparative immunogenicity and safety of refrigerated and frozen formulations of FluMist in individuals 5 to 49 years of age without high risk medical conditions. Nine hundred and eighty-one subjects were randomized at a 1:1 ratio to receive either vaccine formulation. Subjects 5-8 years of age received two doses of study vaccine 46-60 days apart; subjects 9-49 years of age received one dose of study vaccine. The study met its primary endpoint. The GMT ratios of refrigerated and frozen formulations (adjusted for baseline serostatus) for H1N1, H3N2 and B strains, respectively, were 1.24, 1.02 and 1.00 in the two dose group and 1.14, 1.12 and 0.96 in the one dose group.

14.5 Transmission Study

FluMist contains live attenuated influenza viruses that must infect and replicate in cells lining the nasopharynx of the recipient to induce immunity. Vaccine viruses capable of infection and replication can be cultured from nasal secretions obtained from vaccine recipients. The relationship of viral replication in a vaccine recipient and transmission of vaccine viruses to other individuals has not been established.

Using the frozen formulation, a prospective, randomized, double-blind, placebo-controlled trial was performed in a daycare setting in children <3 years of age to assess the transmission of vaccine viruses from a vaccinated individual to a non-vaccinated individual. A total of 197 children 8-36 months of age were randomized to receive one dose of FluMist (n=98) or placebo (n=99). Virus shedding was evaluated for 21 days by culture of nasal swab specimens. Wild-type A (H3N2) influenza virus was documented to have circulated in the community and in the study population during the trial, whereas Type A (H1N1) and Type B strains did not.

At least one vaccine strain was isolated from 80% of FluMist recipients; strains were recovered from 1-21 days post vaccination (mean duration of 7.6 days ± 3.4 days). The cold-adapted *(ca)* and temperature-sensitive (*ts)* phenotypes were preserved in 135 tested of 250 strains isolated at the local laboratory. Ten influenza isolates (9 influenza A, 1 influenza B) were cultured from a total of seven placebo subjects. One placebo subject had mild symptomatic Type B virus infection confirmed as a transmitted vaccine virus by a FluMist recipient in the same playgroup. This Type B isolate retained the *ca*, *ts*, and *att* phenotypes of the vaccine strain, and had the same genetic sequence when compared to a Type B virus cultured from a vaccine recipient within the same playgroup. Four of the influenza Type A isolates were confirmed as wild-type A/Panama (H3N2). The remaining isolates could not be further characterized.

Assuming a single transmission event (isolation of the Type B vaccine strain), the probability of a young child acquiring vaccine virus following close contact with a single FluMist vaccinee in this daycare setting was 0.58% (95% CI: 0, 1.7) based on the Reed-Frost model. With documented transmission of one Type B in one placebo subject and possible transmission of Type A viruses in four placebo subjects, the probability of acquiring a transmitted vaccine virus was estimated to be 2.4% (95% CI: 0.13, 4.6), using the Reed-Frost model.

The duration of FluMist vaccine virus replication and shedding have not been established.

15 REFERENCES

1. Centers for Disease Control and Prevention. Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2007;56(RR-6):1-54.

16 HOW SUPPLIED/STORAGE AND HANDLING

FluMist is supplied for intranasal delivery in a package of 10 pre-filled, single-use sprayers.

NDC 66019-106-01

Storage and Handling

Once FluMist has been administered, the sprayer should be disposed of according to the standard procedures for medical waste (e.g., sharps container or biohazard container).

FLUMIST SHOULD BE STORED IN A REFRIGERATOR BETWEEN 2-8°C (35-46°F) UPON RECEIPT AND UNTIL USE. THE PRODUCT MUST BE USED BEFORE THE EXPIRATION DATE ON THE SPRAYER LABEL.

DO NOT FREEZE.

The cold chain (2 to 8°C) must be maintained when transporting FluMist.

17 PATIENT COUNSELING INFORMATION

Vaccine recipients or their parents/guardians should be informed by the health care provider of the potential benefits and risks of FluMist, and the need for two doses at least 1 month apart in children 2-8 years old who have not previously received influenza vaccine.

17.1 Asthma and Recurrent Wheezing

Ask the vaccinee or their parent/guardian if the vaccinee has asthma. For children <5 years of age, also ask if the vaccinee has recurrent wheezing since this may be an asthma equivalent in this age group.

17.2 Vaccination with a Live Virus Vaccine

Vaccine recipients or their parents/guardians should be informed by the health care provider that FluMist is an attenuated live virus vaccine and has the potential for transmission to immunocompromised household contacts.

17.3 Adverse Event Reporting

The vaccine recipient or the parent/guardian accompanying the vaccine recipient should be told to report any suspected adverse events to the physician or clinic where the vaccine was administered.

FluMist® is a registered trademark of MedImmune, LLC.

MedImmune

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