

## **FluMist™ (Influenza Virus Vaccine Live, Intranasal)**

MedImmune Vaccines, Inc./Wyeth

### ***Background***

Influenza vaccination is the primary method for preventing influenza and its complications, including an average of approximately 36,000 deaths annually in the US between 1990-1999 (1). Annual rates of symptomatic illness, visits to a healthcare provider, and hospitalizations due to influenza have been estimated to be 65 million, 30 million, and 300,000 respectively (2). Persons aged 65 years or older, those having underlying medical conditions, and children ages 0 to 1 year are at greatest risk for serious illness, hospitalization, and death (1). Vaccination reduces influenza-related respiratory illness and physician visits among all age groups, hospitalization and death among persons at high risk, otitis media among children, and work absenteeism among adults (1). Influenza antibody development typically takes 2 weeks after administration. In April 2003, the Advisory Committee on Immunization Practices (ACIP) issued the annual vaccination recommendations for the 2003-2004 influenza season, which parallel those of the previous year (Table 1) (1).

The 2003-2004 vaccines include A/Moscow/10/99 (H3N2)-like, A/New Caledonia/20/99 (H1N1)-like and B/Hong Kong/330/2001-like (1). The optimal time to vaccinate is during October and November; however, vaccination can occur at any time throughout the influenza season. Although the FDA has indicated that vaccine should be in good supply this year, the annual supply and the timing of its distribution are never guaranteed due to the inherent time constraints in manufacturing. Therefore, as with previous years' recommendations, the ACIP recommends that October vaccine campaigns should focus their efforts primarily on the high-risk individuals and target groups (1). Vaccination prior to October is not recommended because antibody levels begin to decline within a limited time after vaccination. For persons not in target groups, the ACIP recommends delaying vaccination until November and beyond.

In the 2003 season, only two companies (Aventis Pasteur, Inc./Fluzone® and Evans Vaccines, Ltd./Fluviron®) will be manufacturing the standard inactivated vaccine in contrast to 3 companies in 2002. Past problems with supply and demand coupled with historically poor vaccination rates has catapulted research into new avenues for vaccination, the first of which was recently approved by the FDA.

### ***Introduction***

FluMist, approved by the FDA in June 2003, is a trivalent, live attenuated influenza vaccine (LAIV) administered intranasally. LAIVs are being used in other countries and have been studied in the US since the 1960s (1). LAIVs consist of live viruses that replicate in the upper respiratory tract, induce minimal symptoms, and replicate poorly the lower temperatures of the lower respiratory tract. FluMist is the first nasally administered vaccine and the first live virus influenza vaccine approved in the U.S.

FluMist is approved to prevent influenza illness due to influenza A and B viruses in healthy children and adolescents, ages 5-17 years, and healthy adults ages 18-49 years. FluMist is *not* indicated for use in children less than 5 years, adults aged 50 years and older, or in persons of any age with chronic underlying medical conditions and immune suppression, including those with asthma or other reactive airway diseases, immune deficiency (e.g persons with HIV or cancer or who are being treated with drugs that cause immunosuppression) because of lack of established safety and efficacy data. Furthermore, in a large safety study, children under 5 years had an increased rate of asthma and wheezing within 42 days of vaccination compared to placebo recipients.

The vaccine administration schedule is similar to the standard intramuscular vaccine- children and adults aged 9-49 years and previously vaccinated children aged 5-8 years require 1 intranasal

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dose per season, whereas children 5-8 years old require 2 doses at least 6 weeks apart in their first year of influenza vaccination. Each dose of FluMist is formulated to contain each of the three influenza virus strains recommended by the U.S. Public Health Service.

### ***Pediatric Efficacy Study (3,4)***

The Pediatric Efficacy Study was a multi-center, randomized, double-blind, placebo controlled trial in healthy children over 2 successive years. During the first year, the primary efficacy endpoint was the 1<sup>st</sup> episode of culture-confirmed influenza. Subjects were randomized to receive a one-dose or two-dose vaccine, with the 2<sup>nd</sup> dose of vaccine administered approximately 60 days after the 1<sup>st</sup> dose. Parents were asked to report any adverse effects and influenza-like symptoms (fever, runny nose, nasal congestion, sore throat, cough, headache, muscle ache, fever, chills, vomiting, suspected/confirmed otitis media, decreased activity, irritability, shortness of breath, pulmonary congestion, or whether child was seen by a PCP and the PCP's diagnosis and antibiotic treatment) via diary and symptom cards during the influenza season in their community. A report of any of flu-like symptom prompted collection of a viral-culture when possible. Influenza was defined as any illness detected by active surveillance that was associated with a positive culture for wild-type influenza virus. In year 2, 1358 (85%) of children, aged 26-85 months, returned for revaccination. Participants were not re-randomized. The primary endpoint was the first episode of culture-confirmed influenza illness occurring after revaccination. A separate immunogenicity study was also performed each year.

Ninety-seven percent of subjects enrolled in the two-dose regimen received both doses; dropouts due to adverse events after 1<sup>st</sup> dose (n=2), withdrawal of consent (n=18), and intercurrent illness (n=7), protocol violation or investigator withdrawal (n=12), and loss to follow-up (n=3). The most common adverse effects were rhinorrhea or nasal congestion on days 1-10 after the 1<sup>st</sup> dose (58% vaccine vs. 47% placebo; p<0.001). Low-grade, fever of short duration was more common on day 2 after the first dose of vaccine, but significant differences were not observed overall (days 1=10). Vomiting was also significantly greater in the vaccine group than placebo group on days 1-10 after the first dose (p=0.03). There were no significant differences in any adverse events after the second dose among vaccine- and placebo recipients.

Primary efficacy results are shown in Table 2. In year 1, FluMist produced a significant 29% relative reduction in the incidence of any febrile illness and concomitant antibiotic use (95% CI 15-39%, p<0.001) and a 35% reduction in otitis media and concomitant antibiotic use (95% CI 18-45%, P<0.001). Two doses were more effective than one, particularly at increasing antibody responses to H1N1. In the immunogenicity substudy, 61% of initially seronegative recipients receiving 2 doses had antibody response to H1N1 and 96% had antibodies to H3N2 and B compared to 2%, 11%, and 3% of placebo recipients respectively (p value not reported).

During the 2<sup>nd</sup> year, the H3N2 strain included in the vaccine was Type A/Wuhan/359/95; however, the epidemic of influenza virus was largely due to a variant H3N2 strain, Type A/Sydney/05/97 not contained in the vaccine. Adverse events including rhinorrhea, fever, or decreased activity did not differ significantly among vaccine and placebo recipients in year 2. The vaccine was 86% efficacious against the variant Sydney virus which caused 66 or 71 cases of influenza. The spectrum of illness was similar to year 1. The duration of fever (2.1 days in vaccine subjects vs. 4.9 days in placebo subjects, p<0.01) was significantly shorter in vaccine recipients. Otitis media and lower respiratory tract illness was also reduced in vaccine subjects. One hundred fifty nine (78%) subjects who participated in the immunogenicity substudy returned in year 2. After revaccination, 82%, 100%, and 100% of subjects in the vaccine group and 20%, 65%, and 46% of placebo recipients had antibody to antigens H1N1, H3N2, and B. The H3N2

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antibodies cross-reacted with a variant influenza that emerged as the major cause of influenza illness in 1997- A/Sydney/5/97. Cross-reactive antibodies were present in 98% and 60% of vaccinated and placebo subjects respectively ( $p < 0.05$ ).

### **Adult Effectiveness Study (5)**

The Adult Effectiveness Study was a multicenter, randomized, double-blind, placebo-controlled trial (5,6). The primary outcomes included: 1) febrile illness- proportion of subjects reporting 1 or more febrile illness during the peak outbreak period (symptoms for at least 2 consecutive days with fever at least on one day, and 2 or more symptoms on at least one day); 2) severe febrile illness-  $\geq 3$  consecutive days of illness,  $\geq 1$  febrile day, and  $\geq$  symptoms on at least 3 days, 3) febrile upper respiratory infection (URI)-  $\geq 2$  consecutive days of URI symptoms,  $\geq 1$  febrile day, and at least 2 URI symptoms on at least 1 day, and 4) work absenteeism/work loss, and healthcare use (PCP visits, antibiotics, and OTC meds) each month from 11/97 to 3/98 self-reported via daily cards. Subjects were randomized 2:1 LAIV to placebo, each supplied in single intranasal dose, self-administered under direct observation or by staff. Regional influenza surveillance was conducted weekly at a designated lab for each center and by CDC to define total and site-specific peak outbreak periods.

Participants were included in the analysis if they provided any follow-up data. Approximately 94% returned the symptom cards during total outbreak period and peak outbreak period. Dropouts included 3 subjects due to adverse events not related to vaccine; 15 due to voluntary withdrawal or noncompliance;  $\sim 2\%$  in each arm were lost to follow-up. Reactogenicity data were available for 98% of each LAIV and placebo group. Subjects who received LAIV were significantly more likely to report runny nose (44.3% LAIV vs. 26.6% P) and sore throat (26.6% LAIV vs. 16.3% P).

The peak outbreak periods lasted a median duration of 7 weeks (4-12 weeks). The total outbreak period for all sites combined was 12/14/97 to 3/21/98 (14 week) and was similar to national data. 99% of isolates from labs were type A and  $> 99\%$  of A subtype was H3N2. The predominant circulating virus was not well matched to the A strain in the vaccine, suggesting LAIV provided cross-protection across the variant strain. Results are presented in Table 3. Overall, the vaccine provided a 10-36% reduction in rates of illness ( $p < 0.002$  for all except  $p = 0.01$  for febrile illnesses), 22.9-27.3% reduction in rates of total days ill ( $p < 0.001$  for all), 13.1-28.4% reduction in rates of work-loss days ( $p < .001$  for all except febrile illness), and 14.7-40.9% reduction in rates of at least 1 healthcare provider visit ( $p < 0.001$  except febrile illness). FluMist also reduced rates of days taking antibiotics and OTC medications.

### **Adult Challenge Study (6)**

In the Adult Challenge Study, 103 healthy subjects aged 18-41 years who were serosusceptible to at least 1 strain included in the vaccine were randomized to receive FluMist (CAIV-T), IM trivalent inactivated vaccine (TIV), or placebo. Prior to vaccination, on the day of challenge, and 28 days after vaccination, sera were obtained to determine antibody response to the 3 components of vaccine. Each subject was challenged intranasally with a single strain of wild-type virus approximately 28 days after vaccination in isolation facilities. Following challenge, subjects were followed daily for the development of signs and symptoms of influenza and daily symptom cards were recorded. Nasal wash samples for virus isolation were obtained daily for 7 days. Vaccination took place 12/95 and the viral challenge took place 1/96.

Runny nose and cough were the most commonly reported adverse events and did not differ significantly among groups. The primary outcome was laboratory-documented influenza

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(respiratory illness and laboratory evidence of wild-type virus infection). Secondary outcomes included wild-type influenza virus infection (virus shedding on one or more days following challenge and/or with a greater than four-fold or greater increase in HAI titer between pre- and post-challenge sera) and respiratory illness (one or more respiratory symptoms of at least level 2 in severity, or two or more respiratory symptoms on any severity on any day, or one or more respiratory symptoms on two or more consecutive days). Results are presented in Table 4. The precision of results is decreased by the small sample size and low rates of infection and illness in placebo-recipients. Additionally, some subjects may have been exposed to virus during the time between vaccination and admission to the challenge facility.

### ***Cost-Effectiveness***

The investigators of the primary pediatric efficacy study also conducted a cost-effectiveness (CE) evaluation (7). The objective was to assess the potential cost-effectiveness of intranasal vaccination, including break-even costs, in healthy children based on data from the pediatric efficacy study. Funding was primarily from the pharmaceutical industry. The analysis compared vaccine with no vaccine, not to the standard inactivated vaccine. Although the primary outcome of the efficacy trial was culture-confirmed influenza, the outcome measure used in the CE analysis was febrile influenza-like illness (ILI). Any child who met any of the five direct medical resource utilization criteria and had a temperature of  $\geq 101\text{F}$  (oral or its equivalent) was considered to have ILI. The main CE analyses were based on two scenarios 1) individual-based vaccination- all caregivers were assumed to initiate a visit to a health care facility specifically for vaccination of a child, 2) group-based vaccination- vaccination performed in a group setting, such as a school or child care facility, eliminating all caregivers' loss of time, productivity, and transportation costs associated with vaccination visits. Per-child CE from the societal perspective was calculated separately for each scenario. The CE averaged over the 2 year period was \$29.67 per ILI fever day avoided. The vaccination cost below which its use would be cost saving was \$28 for group-based vaccination and \$4.93 for individual vaccination. From the perspective of the third party payor, the CE was \$19.10 per ILI fever day avoided for each scenario. The largest changes in CE resulted from increasing the vaccine cost from the individual-based vaccination scenario. The CE changed from \$10 to \$69 per ILI day avoided when the vaccine/administration cost was varied from \$10/dose to \$40/dose.

### ***Conclusion***

Across placebo-controlled trials, FluMist appears to produce protective efficacy rates for influenza to standard inactivated vaccines. Because the safety of FluMist has not been demonstrated in persons with asthma, other chronic medical conditions, or immunosuppression due to any cause or in persons younger than 5 years or over 49 years, the use of FluMist is restricted to a limited population not targeted for routine vaccination campaigns. Standard, inactivated vaccine is preferred in these individuals. The cost of FluMist is approximately \$58 per dose, in comparison to the standard, inactivated vaccine which is typically  $< \$10$  (not including administration costs). The only apparent advantage of LAIV over the inactivated vaccine is its apparent ease of administration and the potential for increased acceptability of an intranasal rather than an intramuscular route of administration.

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**Table 1: ACIP Target Groups for Vaccination Campaigns (1)**

1) groups at greatest risk for influenza-related complications
<ul style="list-style-type: none"> <li>• persons aged ≥65 years and persons of any age with certain chronic medical conditions such as cardiovascular disease, asthma and other chronic respiratory conditions, diabetes, renal dysfunction, hemoglobinopathies, or immunosuppression, children on long-term aspirin therapy</li> <li>• women who will be in the 2<sup>nd</sup> or 3<sup>rd</sup> trimester of pregnancy during the influenza season</li> <li>• residents of nursing homes or other chronic care facilities)</li> </ul>
2) the group aged 50-64 years because this group has an elevated prevalence of certain chronic medical conditions
3) persons who live with or care for persons at high risk (e.g., health-care workers and household contacts who have frequent contact with persons at high risk and who can transmit influenza to persons at high risk)

**Table 2: Pediatric Effectiveness Study: Incidence Of Influenza in Year 1 and Year 2 (3,4)**

Year	Design	Subjects	Treatment Arms	Influenza type	One-Dose Cohort			Two-Dose Cohort			All			
					V (n=189)	P (n=99)	RRR % (95% CI)	V (n=849)	P (n=410)	RRR % (95% CI)	V (n=1070)	P (n=532)	RRR, % (95% CI)	
1	MC, R, DB, PC	Healthy Mean age: 42 mo (15-71)  % Enrolled in daycare or preschool: 64-65%	1 dose: n=288	H3N2 (Wuhan)	2 (1%)	8 (8%)	87 (47-97)	4 (0.5%)	49 (12%)	98 (90-99)	7 (0.6%)	64 (12%)	96 (88-97)	
				H3N2 (Sydney)	-	-	-	-	-	-	-	-	-	-
				B	1 (0.5%)	6 (6%)	91 (46-99)	6 (0.7%)	31 (7.6%)	91 (78-96)	7 (0.6%)	37 (7%)	91 (79-96)	
			2-dose: n=1314	H1N1	0	0	-	0	0	-	0	0	-	
				Any	3 (1.6%)	14 (14%)	89 (65-96)	10 (1.2%)	74 (18%)	94 (88-97)	14 (1.3%)	95 (17.9%)	93 (88-96)	
2		MC, R, DB, PC	Mean days/wk in daycare: 2.4±2.1	1-revacc. dose: n=1358		V (n=917)	P (n=441)	RRR % (95% CI)	-	-	-	V (n=917)	P (n=441)	RRR, % (95% CI)
					H3N2 (Wuhan)	0	4 (0.9%)	100 (54-100)	-	-	-	0	4 (0.9%)	100 (54-100)
					H3N2 (Sydney)	15 (1.6%)	51 (11.6%)	86 (75-92)	-	-	-	15 (1.6%)	51 (11.6%)	86 (75-92)
					H3N1	NR	NR	NR	-	-	-	NR	NR	NR
					B	0	1 (0.2%)	87 (78-95)	-	-	-	0	1 (0.2%)	87 (78-95)
Any	15 (1.6%)		56 (12.7%)	87 (78-93)	-	-	-	15 (1.6%)	56 (12.7%)	87 (78-93)				

MC=multi-center, R=randomized, DB=double-blind, PC=placebo-controlled, V= vaccine, P=placebo, RRR=Relative Risk Reduction NR=not reported, revacc=revaccination

**Table 3: Adult Effectiveness Study (MC, R, DB, PC) (5,6)**

Subjects	Results	LAIV		P		Reduction Rates (%)	P value
		Total n=2874	Rate per 1000 persons per 14-wk period	Total n=1433	Rate per 1000 persons per 14-wk period		
n=4561 Healthy, working adults Mean age: 38 yrs (18-64) % F: 54 % White: 84	<b>Total outbreak period</b>						
	≥1 febrile illness, n	751	276.5	412	302.5	8.6 (-2.0-18)	.11
	Days	6929	2551.3	3886	2853.1	10.6 (-0.7-20.6)	.07
	Days work missed	812	299.0	484	355.3	15.9 (2.9-26.4)	.01
	≥1 healthcare visit	213	78.4	128	94.0	16.5 (3.2-28.0)	.02
	Days taking ABX	1037	381.8	723	530.8	28.1 (16.6-38.0)	<.001
	Days taking OTCs	3163	1164.6	1846	1355.3	14.1 (2.7-24.1)	..02
	<i>Severe febrile illness, n</i>	543	199.9	326	239.3	16.5 (6.2-25.6)	.002
	Days	5945	2189.0	3473	2549.9	14.2 (2.8-24.2)	.02
	Days work missed	717	264.0	454	333.3	20.8 (9.2-30.9)	<.001
	≥ 1 healthcare visit	191	70.3	124	91.0	22.8 (10.3-33.4)	<.001
	Days taking ABX	957	352.4	684	502.2	29.8 (18.5-39.6)	<.001
	Days taking OTCs	2757	1015.2	1681	1234.2	17.7 (6.4-27.7)	.003
	<i>Febrile URI, n</i>	472	173.8	285	209.2	16.9 (6.5-26.2)	.002
	Days	5047	1858.4	2873	2109.4	11.9 (-0.1-22.4)	.05
	Days work missed	530	195.1	365	268.0	27.2 (16.1-36.8)	<.001
	≥1 healthcare visit	142	52.3	98	72.0	27.3 (15.2-37.7)	<.001
	Days taking ABX	793	292.0	553	406.0	28.1 (16.0-38.4)	<.001
	Days taking OTCs	2345	863.4	1483	1088.8	20.7 (9.7-30.4)	<.001
	<b>Peak outbreak period</b>	Total n=2833	Rate per 1000 persons per 7-wk period	Total n=1420	Rate per 1000 persons per 7-wk period		
	≥1 febrile illness, n	406	151.3	225	168.1		
	Days	3188	1188.0	2063	1541.2	10.0 (-2.1-20.7)	0.10
	Days work missed	465	173.3	267	199.5	22.9 (11.1-32.4)	<.001
	≥1 healthcare visit	118	44.0	69	51.5	13.1 (-0.9-25.2)	.07
	Days taking ABX	525	195.6	459	342.9	14.7 (-0.3-27.5)	.06
	Days taking OTCs	1548	576.9	1007	752.3	42.9 (33.1-51.3)	<.001
	<i>Severe febrile illness</i>	298	111.0	183	136.7	23.3 (12.0-33.2)	<.001
	Days	2740	1021.1	1880	1404.5	18.8 (7.4-28.8)	.002
	Days work missed	415	154.6	252	188.3	27.3 (16.7-36.5)	<.001
	≥ 1 healthcare visit	101	37.6	67	50.1	17.9 (4.3-29.5)	.01
	Days taking ABX	462	172.2	435	325.0	24.8 (1.6-36.1)	<.001
	Days taking OTCs	1358	506.1	935	698.5	47.0 (37.8-54.9)	<.001
	<i>Febrile URI</i>	248	92.4	162	121.0	27.6 (16.5-37.1)	<.001
Days	2350	875.7	1559	1164.7	23.6 (12.7-33.2)	<.001	
Days work missed	287	107.0	200	149.4	24.8 (13.5-34.7)	<.001	
≥ 1 healthcare visit	64	23.08	54	40.3	28.4 (16.3-38.8)	<.001	
Days taking ABX	376	140.1	342	255.5	40.9 (30.1-50.0)	<.001	
Days taking OTCs	1186	442.0	822	614.1	45.2 (35.2-53.6)	<.001	

LAIV=3 live attenuated influenza virus strains H1N1, H3N2, and SPG antigenically equivalent to the inactivated vaccine for 97-98

Rates=(counts/total subject days) x 7 days/wk x 7 (or 14) weeks per outbreak period x 1000 persons

**Table 4: Pooled Results Adult Effectiveness Study (6)**

Vaccine	N	Virus shedding <sup>a</sup>	OR (95% CI)	Antibody Response <sup>b</sup>	Virus infection <sup>c</sup>	OR (95% CI)	Laboratory documented influenza <sup>d</sup>	OR (95% CI)
CAIV-T	29	7 (24%)	0.64 (0.16-2.3)	6 (21%)	9 (31%)	0.35 (0.10-1.1)	2 (7%)	0.10 (0.01-0.52)
TIV	32	5 (16%)	0.36 (0.08-1.4)	0	5 (16%)	0.14 (0.03-0.56)	4 (13%)	0.18 (0.04-0.70)
Placebo	31	10 (32%)	-	13 (42%)	17 (55%)	-	14 (45%)	-

A Shedding of wild-type virus on one or more days following challenge

B 4-fold or greater serum antibody response comparing pre- and post-challenge data

C Virus shedding, antibody response or both.

D Respiratory illness (one or more respiratory symptoms of at least level 2 in severity, or two or more symptoms of any severity on any day, or one or more symptoms on two or more consecutive days).