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FluMist: New Flu Option Not Recommended For High Risk Patients

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Vaccination is the primary method for preventing influenza (flu) and its complications. Vaccination reduces flu-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 (1). In April 2003, the Advisory Committee on Immunization Practices (ACIP) issued the annual vaccination recommendations for the 2003-2004 flu season, which parallel those of the previous year (Table 1) (1). The optimal time to vaccinate is during October and November; however, vaccination can occur at any time during the flu season. The FDA predicts adequate vaccine supply this year but it cannot be guaranteed due to manufacturing limitations. Two companies (Aventis Pasteur, Inc./Fluzone® and Evans Vaccines, Ltd./Fluviron®) are manufacturing the standard, intramuscular trivalent inactivated vaccine (TIV) in contrast to 3 companies in 2002. Past problems with supply and demand coupled with historically poor vaccination rates has resulted in increased research into new vaccine products.

Table 1: ACIP 2003-2004 Influenza Season Recommendations (1)

Composition of the vaccine	1) A/Moscow/10/99 (H3N2)-like 2) A/New Caledonia/20/99 (H1N1)-like 3) B/Hong Kong/330/2001-like
ACIP target groups for vaccination campaigns	1) Persons at greatest risk for flu-related complications - Persons aged ≥65 years - All persons with certain chronic medical conditions (e.g. cardiovascular disease, asthma and other chronic respiratory conditions, diabetes, renal dysfunction, hemoglobinopathies, or immunosuppression) - Children on long-term aspirin therapy - Women in the 2nd or 3rd trimester of pregnancy - Residents of nursing homes/chronic care facilities 2) Persons aged 50-64 years 3) Persons who live with or care for persons at high risk (e.g. health-care workers, household contacts)
Administration schedule	1) 1 Dose - Persons aged 9-49 yrs - Previously vaccinated children aged 5-8 yrs 2) 2 Doses ≥ 6 weeks apart - Previously unvaccinated children aged 5-8 yrs

FluMist, approved June 2003, is a nasally administered trivalent, live attenuated flu vaccine which replicates in the upper respiratory tract, inducing minimal symptoms, and replicates poorly in the temperatures of the lower respiratory tract. Each dose of FluMist is formulated to contain each of the three virus strains recommended by the U.S. Public Health Service and ACIP. FluMist is approved to prevent illness due to influenza A and B in healthy children and adolescents, aged 5-17 yrs, and healthy adults aged 18-49 yrs. The safety and efficacy of FluMist has not been evaluated or demonstrated in high-risk target groups. Table 2 provides a summary of persons for whom FluMist is indicated. The administration schedule is the same as TIV.

Table 2: Persons for Whom FluMist *Is* and *Is Not* Indicated

Indicated	*Not* Indicated
• *Healthy* children, adolescents - 5-17 yrs • *Healthy* adults - 18-49 yrs	• Children < 5 yrs • Adults ≥ 50 yrs • Pregnant women • Persons of any age with underlying medical conditions or immune suppression: - Asthma, COPD, or other reactive airway disease - Cardiovascular disease - Diabetes - Immunosuppressive drug therapy - Cancer - HIV/AIDs

Clinical Trial: Pediatric Efficacy Study (3,4)

The Pediatric Efficacy Study was a multi-center, randomized, double blind and placebo-controlled trial in healthy children over 2 successive years. Approximately 65% of subjects were enrolled in daycare or preschool for a mean number of 2.4±2.1 days/week. The primary endpoint was the first episode of culture-confirmed flu. Subjects were randomized to receive vaccine or placebo in a 1-dose or 2-dose regimen, in which the second dose was given approximately 60 days after the first dose in year 1. All subjects were invited to return the following year for a 1-dose revaccination study.

Results are shown in Table 3. Overall in the first year, FluMist was 93% effective for culture-confirmed flu. Two doses were more effective than one - 94% vs. 89%, respectively. 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). During the 2nd-year, FluMist was 86% effective against the variant Sydney virus not contained in the vaccine. The duration of fever, otitis media, and lower respiratory tract illness was reduced in vaccine subjects.

Table 3 - Combined Results for Primary Endpoint

Study Period	Treatment	Culture-Confirmed Influenza, n (%)	RRR (95% CI)
Year 1	FluMist (n=1070)	14 (1.3)	93% (88-96%)
	Placebo (n=532)	95 (17.9)	
Year 2	FluMist (n=917)	15 (1.6)	87% (78-93%)
	Placebo (n=441)	56 (12.7)	

Clinical Trial: Adult Effectiveness Study (5)

The Adult Effectiveness Study was a multi-center, randomized, double blind, placebo-controlled trial in healthy, working adults aged 18 to 64 years (5). Pregnant women and persons with high-risk medical conditions or positions of employment were excluded. Subjects were randomized to receive a single intranasal dose of FluMist or placebo. The primary

endpoint was the proportion of subjects reporting ≥ 1 febrile illness during the site-specific, peak outbreak period. Additional outcomes included the incidence of severe febrile illness, febrile upper respiratory illness (URI), work absenteeism/work loss, and healthcare use (visits to a healthcare provider and use of antibiotics and OTC drugs). Subjects with no follow-up data available (~ 6%) were excluded from the analyses.

Results are presented in Table 4. FluMist was not effective for the primary outcome during the peak (~7 wk) or total (~12 wk) outbreak periods; however, it was effective in reducing the incidence of severe febrile illness (16.5-18.8% RRR; p=.002) and febrile URI (16.9-23.6% RRR, p<.001). FluMist significantly reduced lost workdays, healthcare provider visits, and use of antibiotics and OTC drugs during peak and total outbreak periods.

Table 4: Results for Site-Specific Peak Outbreak Period

Outcome	FluMist N / rate per 1000 (total n = 2833)	Placebo N /rate per 1000 (total n = 1420)	Reduction Rates %	P value
≥1 febrile illness	406 /151.3	225 /168.1	10.0 (-2.1-20.7)	0.10
Severe febrile illness	298 /111.0	183 /136.7	18.8 (7.4-28.8)	.002
Febrile URI	248 /92.4	162 /121.0	23.6 (12.7-33.2)	<.001

Adult Challenge Study (6)

In the Adult Challenge Study, 103 healthy subjects aged 18-41 years who were serosusceptible to at least 1 strain in the vaccine were randomized to receive FluMist, TIV, or placebo. Each subject was then challenged intranasally approximately 28 days after vaccination in isolation facilities with a single strain of wild-type virus to which he/she was previously susceptible.

The primary outcome was laboratory-documented flu (respiratory illness and laboratory evidence of wild-type virus infection). Results are presented in Table 5. FluMist and TIV reduced the incidence of laboratory-documented flu compared to placebo. There were no significant differences in the incidence of laboratory-documented flu among vaccines. The precision of results is decreased by the small sample size, low rates of infection and illness in placebo-recipients, and the potential for virus exposure during the time between vaccination and admission to the challenge facility.

Safety

Overall, FluMist was well tolerated. In healthy children, the most common adverse events included rhinorrhea/nasal congestion on days 1-10 after the 1st dose (58% vaccine vs. 47% placebo; p<0.001), low grade fever, cough, irritability, headache, decreased activity, sore throat, fever, muscle aches and chills (3,4). An increased rate of asthma and wheezing within 42 days of vaccination compared to placebo recipients was observed in children < 5 years old. Adverse events reported in adults were similar and included rhinorrhea (44.3% FluMist vs. 26.6% placebo), sore throat (26.6% FluMist vs. 16.3% placebo), headache, tiredness/weakness, muscle aches, cough and chills (5). All events were transient.

Conclusion

Across placebo-controlled trials, FluMist appears to produce protective efficacy rates for flu when compared to standard inactivated vaccines. Because the safety of FluMist has not been demonstrated in persons with asthma, other chronic medical conditions, immunosuppression due to any cause, pregnant women, or persons < 5 years or > 49 years, the standard TIV is recommended in these individuals. In addition, because FluMist contains live influenza virus, a potential though small risk, exists for transmission of these viruses from vaccine recipients to other persons. The cost of FluMist is approximately $58 per dose, in comparison to TIV, typically < $10 (not including administration costs) (7). The only apparent advantage of FluMist over TIV is the potential for increased acceptability of an intranasal rather than an intramuscular route of administration. FluMist should be reserved for patients who do not have sufficient muscle mass for administration of TIV.

Reviewed by: Sarah Slaughter, MD; Infectious Disease

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Table 5: Adult Challenge Study

Vaccine	N=	Virus shedding[a]	OR (95% CI)	Antibody Response[b]	Virus infection[c]	OR (95% CI)	Laboratory documented influenza[d]	OR (95% CI)
FluMist	29	7 (24%)	0.64 (0.16-2.3)	6 (21%)	9 (31%)	0.35 (0.10-1.1)	2 (7%)	0.1 (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).

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