

Rapid Protocol Safely Jump-Starts Allergy Shots

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BOSTON — A new immunotherapy protocol can substantially and safely reduce the amount of time it takes for children with allergies to experience relief from their symptoms, compared with conventional allergen vaccination, reported William Smits, M.D.

In addition to saving time and money, the compressed vaccination schedule ap-

pears to improve patient compliance, Dr. Smits said in a presentation at the annual meeting of the American College of Allergy, Asthma, and Immunology.

A type of "rush" regimen, this is a novel protocol that jump-starts allergy immunotherapy with a series of in-office vaccinations given over a 2.5-hour period. Unlike other rapid desensitization efforts—many of which have been shown to evoke serious systemic reactions in a large proportion of patients—this protocol in-

cludes 3 days of premedication with corticosteroids and H1 antagonists to minimize the potential for adverse reactions.

"Previous studies [of rapid vaccination regimens] have shown reaction rates of anywhere from 30% to 40%, which is the major concern with rush protocols," said Dr. Smits of Indiana University, Fort Wayne. "With our approach, we've found a rate close to that of conventional immunotherapy."

Dr. Smits and his colleagues tested the

rapid vaccination protocol in 148 children aged 1-18 years diagnosed with mild to severe asthma (118), allergic rhinitis (143), and/or chronic sinusitis (23). All of the children were pretreated for 3 days with prednisone or prednisolone and second-generation antihistamines, including cetirizine (Zyrtec), loratadine (Claritin), and fexofenadine (Allegra). On the vaccination day, the children received eight injections given at 15-minute intervals. The doses increased from an initial 1:1,000,000 dilution to a final 1:1,000 dilution.

In addition to premedication, a key to the success of this treatment is lowering the target end point dosage, said Dr. Smits.

The harmful reactions reported in earlier studies generally occurred at the end of the rapid treatment phase, when the patient received a final high dose to be maintained for the duration of the therapy. "We stopped just before that time and gave the patients the last injections over a 2-month period."

The investigators monitored the children for systemic reactions. Of the full cohort, eight patients—seven of whom were asthma patients on inhaled corticosteroids—experienced a systemic reaction following the vaccination. None of the eight patients experienced true anaphylaxis. The patients who had reactions were treated with one or a combination of the following: nebulized breathing treatment with albuterol, two sprays in each nostril of azelastine (Astelin), and diphenhydramine (Benadryl), either orally or intramuscularly. None of the patients requiring treatment needed subcutaneous epinephrine or further treatment for recurrent symptoms. Also, none needed hospitalization.

Following the rapid protocol, all of the patients in the study continued with a conventional allergen immunotherapy regimen to reach their maintenance dose.

"Overall, the patients reached efficacious dosages almost immediately," said Dr. Smits, who estimated the average amount of build-up time saved by the new protocol to be about 6 months. "And adherence rates were better than what we typically see with conventional immunotherapy," he said. Patient adherence rates were 95.3%, 90.5%, and 79.7% at 3, 6, and 12 months, respectively, compared with approximately 50% adherence associated with conventional immunotherapy.

"Contrary to what everyone thinks, there is a way to do this safely," said Dr. Smits, who uses the rapid protocol in approximately 75% of the adults and children he treats.

The bottom line, he concluded, is that the rapid protocol "costs less, incidents of illness are reduced, and people see results more quickly."

FluMist Influenza Virus Vaccine Live, Intranasal

2004-2005 Formula
FOR NASAL ADMINISTRATION ONLY

Rx only
Brief Summary of Prescribing Information

INDICATIONS AND USAGE

FluMist is indicated for active immunization for the prevention of disease caused by influenza A and B viruses in healthy children and adolescents, 5-17 years of age, and healthy adults, 18-49 years of age.

FluMist is not indicated for immunization of individuals less than 5 years of age, or 50 years of age and older, or for therapy of influenza, nor will it protect against infections and illness caused by infectious agents other than influenza A or B viruses.

CONTRAINDICATIONS

Under no circumstances should FluMist be administered parenterally.

Individuals with a history of hypersensitivity, especially anaphylactic reactions, to any component of FluMist, including eggs or egg products, should not receive FluMist.

FluMist is contraindicated in children and adolescents (5-17 years of age) receiving aspirin therapy or aspirin-containing therapy, because of the association of Reye syndrome with aspirin and wild-type influenza infection.

FluMist should not be administered to individuals who have a history of Guillain-Barré syndrome.

As with other live virus vaccines, FluMist should not be administered to individuals with known or suspected immune deficiency diseases such as combined immunodeficiency, agammaglobulinemia, and thymic abnormalities and conditions such as human immunodeficiency, malignancy, leukemia, or lymphoma. FluMist is also contraindicated in patients who may be immunosuppressed or have altered or compromised immune status as a consequence of treatment with systemic corticosteroids, alkylating drugs, antimetabolites, radiation, or other immunosuppressive therapies.

WARNINGS

The safety of FluMist in individuals with asthma or reactive airways disease has not been established. In a large safety study in children 1-17 years of age, children <5 years of age who received FluMist were found to have an increased rate of asthma within 42 days of vaccination when compared to placebo recipients (see ADVERSE REACTIONS). FluMist should not be administered to individuals with a history of asthma or reactive airways disease.

The safety of FluMist in individuals with underlying medical conditions that may predispose them to severe disease following wild-type influenza infection has not been established. FluMist is not indicated for these individuals. High-risk individuals include, but are not limited to, adults and children with chronic disorders of the cardiovascular and pulmonary systems, including asthma; pregnant women; adults and children who require 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 (see CONTRAINDICATIONS). Intramuscularly administered inactivated influenza vaccines are available to immunize high-risk individuals.

As with any vaccine, FluMist may not protect 100% of individuals receiving the vaccine.

PRECAUTIONS

General: CARE IS TO BE TAKEN BY THE HEALTH CARE PROVIDER FOR THE SAFE AND EFFECTIVE USE OF THIS PRODUCT. Prior to administration of FluMist, individuals or their parent/guardian should be asked about their current health status and their personal medical history, including immune status, to determine the existence of any contraindications (see CONTRAINDICATIONS AND WARNINGS) to immunization with FluMist. FluMist recipients should avoid close contact (e.g., within the same household) with immunocompromised individuals for at least 21 days. FLUOROPHENYLACETONE (1:1000) OR COMPARABLE TREATMENT MUST BE READILY AVAILABLE IN THE EVENT OF AN ACUTE ANAPHYLACTIC REACTION FOLLOWING 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 and egg products. Administration of FluMist should be postponed until after the acute phase (at least 72 hours) of febrile and/or respiratory illnesses.

Information for Vaccine Recipients or Parents/Guardians: 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 for the first use of FluMist in 5-8 year olds. Due to the possible transmission of vaccine virus, vaccine recipients or their parents/guardians should be advised to avoid close contact (e.g., within the same household) with immunocompromised individuals for at least 21 days. 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 (see ADVERSE EVENT REPORTING). Drug Interactions: Children or adolescents who are receiving aspirin therapy or aspirin-containing therapy should not receive FluMist (see CONTRAINDICATIONS). FluMist should not be administered to persons on immunosuppressive therapy. The concurrent use of FluMist with antiviral compounds that are active against influenza A and/or B viruses has not been evaluated. However, based upon the potential for interference between such compounds and FluMist, it is advisable not to administer FluMist until 48 hours after the cessation of antiviral therapy and that antiviral agents not be administered until two weeks after administration of FluMist unless medically indicated.

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

Concurrent Administration with Other Vaccines: The safety and immunogenicity of FluMist when administered concurrently with other vaccines have not been determined. Therefore, FluMist should not be administered concurrently with other vaccines. Studies of FluMist in healthy individuals excluded subjects who received any live virus vaccine within one month of enrollment and any inactivated or subunit vaccine within two weeks of enrollment; therefore, health care providers should adhere to these intervals when administering FluMist.

Laboratory Interactions: Data related to the length of time that FluMist can be recovered from nasal specimens of children and adults are limited. Nasopharyngeal secretions or swabs collected from vaccinees may test positive for influenza virus for up to three weeks.

Carcinogenesis, Mutagenesis, Impairment of Fertility: FluMist has not been evaluated for its carcinogenic or mutagenic potential or its potential for impairment of fertility.

Pregnancy (Category C): 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 affect reproduction capacity. Therefore, FluMist should not be administered to pregnant women.

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.

Pediatric Use: The safety of FluMist in infants and children <60 months of age has not been established.

Geriatric Use: Clinical studies with FluMist did not include sufficient numbers of adults age 65 years and older to determine if they respond differently from younger individuals. The safe use of FluMist in persons 65 years and older has not been established.

ADVERSE REACTIONS

Serious Adverse Events: Across all clinical trials, serious adverse events (SAEs) were monitored after vaccination for 42 days in children and for 28 days in adults. SAEs occurred at a similar rate (<1%) in FluMist and placebo recipients for both healthy children and healthy adults.

Overall, across the placebo-controlled trials in adults and children, the incidence of selected adverse reactions that may be complications of influenza (such as pneumonia, bronchitis, bronchiolitis, or central nervous system events) was similar in FluMist and placebo groups.

Adverse Events in Placebo-Controlled Trials: In all placebo-controlled trials, allantoic fluid from uninfected eggs was used as the adjuvant. In randomized, placebo-controlled trials, 4,719 healthy children 5-17 years of age and 2864 healthy adults 18-49 years of age received FluMist and 2,327 healthy children and 1,454 healthy adults received the placebo. In placebo-controlled clinical trials conducted in healthy populations, solicited adverse events and daily temperatures were collected on diary cards. These solicited events included runny nose/nasal congestion, sore throat, cough, irritability, headache, chills, vomiting, muscle aches, and decreased activity and a feeling of tiredness/weakness.

Solicited Adverse Events in Children: Table 1 shows an analysis of solicited events for the Pediatric Efficacy Study in the subset of healthy children (5-17 years of age). The largest absolute differences between FluMist and placebo after Dose One were observed in the incidences of headache and runny nose/nasal congestion. No differences were observed for fever >100°F oral. Following Dose Two, the largest absolute differences between FluMist and placebo were runny nose/nasal congestion and cough; there was a significant increase in influenza-like illness (ILI) as defined by the CDC in the FluMist group compared to the placebo group. CDC has defined CDC-ILI as having fever (temperature >100°F oral) plus either cough or sore throat on the same day or on consecutive days.

Table 1: Summary of Solicited Events Observed within 10 Days after Each Dose for Vaccine and Placebo Recipients, Healthy Children 60-71 Months of Age

Event	Post-Dose One		Post-Dose Two	
	FluMist N=214	Placebo N=95	FluMist N=214	Placebo N=95
Any event	65.4	61.4	66.5	53.3
Cough	26.8	22.7	36.3	39.3
Runny Nose/Nasal Congestion	48.1	44.2	46.0	32.0
Sore Throat	12.6	19.8	9.3	16.0
Irritability	19.5	16.8	9.8	18.3
Headache	17.8	11.6	8.8	16.0
Chills	6.1	5.3	2.5	4.0
Vomiting	4.7	4.2	5.6	12.0
Muscle Aches	6.1	4.2	6.0	10.0
Decreased Activity	14.0	12.6	10.6	13.3
Fever*	9.5	9.9	4.3	4.0
Temp 1	2.2	2.0	0.6	1.3
Temp 2	0.0	0.0	0.0	0.0
Temp 3	0.0	0.0	0.0	0.0

* Denotes statistically significant differences in any of these events (p-value >0.05); Fisher's exact method.

* Number of evaluable subjects (those who returned diary cards) for each event.

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.

For the cohort of 128 children who received FluMist Influenza Virus Vaccine Live, Intranasal across three consecutive years, rates of solicited adverse events were not significantly increased when compared to placebo recipients.

Medically Attended Events in Children and Adolescents: A large randomized, double-blind, placebo-controlled trial in healthy children 1 through 17 years of age 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. Participants were randomized 2:1 (vaccine:placebo). A total of 6657 evaluable children 5-17 years of age were enrolled, including 3244 boys and 3413 girls. Of these 6657 children, 2606 were 5-8 years of age and 4051 were 9-17 years of age. Dose Two for children less than nine years of age was to be administered 28 to 42 days after Dose One.

Data regarding MAEs were obtained from the Kaiser-Permanente computerized health care utilization databases for hospitalizations, emergency department visits and clinical visits. MAEs were analyzed individually and within four pre-specified groups: acute respiratory tract events, systemic bacterial infections, acute gastrointestinal tract events, and rare events potentially related to influenza. For these four pre-specified group diagnoses, no significant increase in risk for FluMist recipients was seen in the combined analyses across all utilization settings, doses, and age groups. Selected respiratory tract illnesses of special interest (pneumonia, bronchitis, bronchiolitis, and croup) were included in acute respiratory tract events and were not associated with increased risk for FluMist recipients in any protocol-specified analysis. No systemic bacterial infection occurred. In FluMist recipients, an increased risk was not observed for rare events that have been reported with naturally occurring influenza virus infection, including seizures, febrile seizures, and epilepsy. No cases of encephalitis, acute idiopathic polyneuritis (Guillain-Barré syndrome), Reye syndrome, or myocarditis (influenza-associated rare disorders) were reported in this study.

In this study, in individuals 5-17 years of age, four individual MAEs were significant (p < 0.05) and 11 were significantly decreased. Of the four individual MAEs associated with increased risk, a biological association with FluMist is plausible for one: abdominal pain. Of the 11 individual MAEs associated with decreased risk, a biologically plausible association with FluMist exists for seven: asthma, bronchitis, cough, viral infection, croup, viral infection, and wheezing/shortness of breath. However, in the same study, a statistically significant increase in asthma or reactive airways disease was observed for children 12-59 months of age following Dose One (Relative Risk 3.53, 90% CI: 1.1, 15.7). As a result of this finding, FluMist is not indicated for children <60 months of age.

Solicited Adverse Events in Adults: In the placebo-controlled Adult Effectiveness Study, the rate of solicited adverse events in the subset of healthy adults 18-49 years of age are shown in Table 2. Statistically significant differences were observed for rare events, such as cough, runny nose, sore throat, chills, and tiredness/weakness. Fever >100°F was similar in FluMist and placebo recipients after Dose One. There was no significant increase in ILI as defined by the CDC in the FluMist group compared to the placebo group.

Table 2: Summary of Solicited Events Observed within 7 Days after Each Dose for Vaccine and Placebo Recipients, Healthy Adults 18-49 Years of Age

Event	FluMist N=2548		Placebo N=1290	
	(%)	(%)	(%)	(%)
Any event	71.9*	62.6	62.6	53.3
Cough	21.9*	17.1	17.1	16.0
Runny Nose	44.5*	37.1	37.1	27.1
Sore Throat	27.8*	21.1	21.1	16.0
Headache	30.4	27.1	27.1	16.0
Chills	6.6*	6.0	6.0	4.0
Muscle Aches	16.7*	14.6	14.6	10.0
Tiredness/Weakness	22.7*	21.1	21.1	16.0
Fever*	1.5	1.3	1.3	1.3
Oral Temp >100°F	0.1	0.0	0.0	0.0
Oral Temp >102°F	0.1	0.0	0.0	0.0
Oral Temp >103°F	0.0	0.0	0.0	0.0

* Denotes statistically significant p-value < 0.05; no adjustments for multiple comparisons; Fisher's exact method.

* Number of evaluable subjects (those who returned diary cards); [97.9% of FluMist recipients and 97.9% of placebo recipients.]

Other Adverse Events in Children and Adults: In addition to the solicited events, parents of subjects in the Pediatric Efficacy trial also reported other adverse events that occurred during the course of the trial. Among healthy children age 60-71 months, the events that occurred in at least 1% of FluMist recipients and at a higher rate compared to placebo were: abdominal pain (3.7% FluMist vs 0% placebo), otitis media (1.4% FluMist vs 0% placebo), accidental injury (2.3% FluMist vs 2.1% placebo), diarrhea (0.7% FluMist vs 1.1% placebo), following Dose One and otitis media (2.1% FluMist vs 1.3% placebo) following Dose Two. None of these differences were statistically significant. In addition to the solicited events, adults who participated in the Adult Effectiveness Study also reported other adverse events that occurred during the course of the clinical trial. For adults 18-49 years of age in the Adult Effectiveness Study, nasal congestion (6.2% FluMist vs 2.2% placebo), rhinitis (6.2% FluMist vs 5.1% placebo), and sinusitis (4.1% FluMist vs 2.2% placebo) were reported significantly more often in FluMist recipients compared to placebo recipients.

Adverse events reported post-study have included nausea, rash, hypersensitivity reactions (including anaphylaxis, facial edema, and urticaria). These events occurred at similar rates in FluMist versus placebo recipients in pre-clinical studies.

Annually, 20-40 cases of Guillain-Barré syndrome (GBS) that occur within 42 days of administration of inactivated influenza vaccine are reported to VAERS. In 2003-2004, one case of GBS with temporal association with FluMist was reported. Evidence of a causal relationship between influenza vaccines, including FluMist, has not been established.

ADVERSE EVENT REPORTING

Reporting by vaccine recipients or the parents/guardians of vaccinees and health care providers of all adverse events occurring after vaccine administration is encouraged. The U.S. Department of Health and Human Services (DHHS) has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine. 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.org>.

DOSEAGE AND ADMINISTRATION

FOR NASAL USE ONLY DO NOT ADMINISTER PARENTERALLY.

FluMist* should be administered according to the following schedule:

Age Group	Vaccination Status	Dosage Schedule
Children age 5 years through 8 years	Not previously vaccinated with FluMist	2 doses (0.5 mL each, 60 days apart ± 14 days) for initial season
Children age 5 years through 8 years	Previously vaccinated with FluMist	1 dose (0.5 mL) per season
Children and Adults age 9 through 49 years	Not applicable	1 dose (0.5 mL) per season

For healthy children age 5 years through 8 years who have not previously received FluMist vaccine, the recommended dosage schedule for nasal administration is one 0.5 mL dose followed by a second 0.5 mL dose given at least 6 weeks later. Only limited data are available on the degree of protection in children 5-8 years of age who have previously received at least one dose of FluMist; the recommended schedule is one dose.

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FluMist should be administered prior to exposure to influenza. The peak of influenza activity is variable from year to year, but generally occurs late in the U.S. between late December and early March. Because the duration of protection induced by FluMist is not known and yearly antigenic variation in the influenza strains is possible, annual revaccination may increase the likelihood of protection.

Based on FluMist Prescribing Information dated September 2004.

Manufactured and Marketed by:
Medimmune Vaccines, Inc.
Gaithersburg, MD 20878

Medimmune
Vaccines, Inc.

U.S. Govt. License No. 1652
Issue Date: September 2004

FLU04-229

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