Influenza Vaccine

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Flu

INTRODUCTION

Influenza is an acute, contagious, and self-limited disease that directly affects the respiratory tract.1 Approximately 10% to 20% of Americans experience illness because of influenza each year;2 resulting in a significant loss in work and productivity that directly and indirectly translates into financial costs. Each year, from $3 billion to $15 billion is spent on total health care costs arising from influenza, and 70 million school days and 38 million school days are missed.3,4

Influenza is responsible for approximately 36,000 deaths and 114,000 hospital admissions every year. Rates of infection are highest among children between five and 14 years of age, but the most severe illnesses and greatest number of deaths occur in people with underlying medical conditions (e.g., cardiovascular and pulmonary illnesses), children under age two years, and people over the age of 65.5,6,7

The influenza virus is spread when a person inhales droplets that have been released through aerosolized secretions of an infected individual. Generally, there is a one- to two-day incubation period from the time of initial exposure to the development of symptoms.1,3 Common signs and symptoms of influenza include a high-grade fever (100.4°F to 105.8°F), chills, sweating, myalgias, dry cough, nasal congestion, headache, fatigue, and malaise.1,3,4 The illness typically lasts for three to five days and, in some cases, persists for up to one to two weeks.3

Although prophylactic antiviral medications are available, vaccination remains the single most effective method of preventing influenza, its complications, and death.3–5 Each year, influenza vaccines are standardized and consist of two types of influenza A strains and one type of influenza B strain, as determined by worldwide surveillance and antigenic characteristics. On the basis of recommendations made by the U.S. Public Health Service (USPHS), the following strains were included in the 2003–2004 vaccines: (1) A/New Caledonia/20/99 (H1N1), (2) A/Panama/2007/99 (H3N2), and (3) B/Hong Kong/330/2001.5,8

The optimal time for obtaining an influenza vaccination is during the months of October and November because the annual peaks of infection occur during the later months of December through March. Currently, two types of vaccines are available in the U.S.: (1) inactivated influenza vaccine (e.g., Fluzone®, Aventis Pasteur, and Fluvirin®, Evans) and (2) live, attenuated influenza vaccine (FluMist™, MedImmune/Wyeth).4,8

FluMist™ was approved by the U.S. Food and Drug Administration (FDA) in June 2003. This new intranasal vaccine is indicated for active immunization against influenza A and B viruses in healthy people between the ages of five and 49. This is the first live virus influenza vaccine to receive FDA approval in the U.S., and it is the first vaccine to be administered intranasally.3,4,8

PHARMACOLOGY AND MECHANISM OF ACTION

FluMist™ is an intranasal, live, attenuated, trivalent, cold-adapted, and temperature-sensitive vaccine.4,8,9 The immune mechanisms that confer protection against influenza following administration of this vaccine are not fully understood, and naturally acquired immunity to wild-type influenza has not been completely clarified. It is possible that serum antibodies, mucosal antibodies, and influenza-specific T cells might be involved in the prevention of and recovery from infection.5,10,11 Vaccination with FluMist™ has been demonstrated to induce influenza strain-specific serum antibodies.3,12,13

The live, attenuated influenza viruses that are present in the vaccine replicate in the nasopharynx of the recipient and are shed in viral secretions. As a result of the vaccine’s cold-adapted and temperature-sensitive properties, the viruses do not gain entry into the lower respiratory tract and do not allow for the replication of different wild-type viruses. Therefore, the risk for transmission of the vaccine viruses from a recipient to another individual is low.3,8

PHARMACOKINETICS

Protective antibody levels are generally achieved approximately two weeks after initial vaccination with FluMist™ and can persist for a period of six months or longer.3,8

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Clinical Trials

The efficacy and safety of FluMist™ have been demonstrated in various clinical trials.

The Pediatric Efficacy Study5,14,15

The Pediatric Efficacy Study was a multicenter, randomized, double-blind, placebo-controlled trial that evaluated the efficacy of FluMist™ against culture-confirmed influenza. This trial was performed over two seasons and included healthy children throughout the U.S. The primary endpoint was the prevention of culture-confirmed influenza caused by antigenically matched, wild-type virus in healthy children who received two doses of the vaccine during the first year of the study.

A group of 312 children between 60 and 71 months of age were randomly assigned to receive the vaccine or a placebo (in a ratio of 2:1). At the conclusion of the study, the overall efficacy of FluMist™ was 87.4% (95% confidence interval [CI]: 59.4, 97.9; P ≤ .05) in the incidence of the study, the overall efficacy of placebo (in a ratio of 2:1). At the conclusion of the study, the overall efficacy of FluMist™ was 87.4% (95% CI: 70.8, 94.1; P ≤ .05), regardless of antigenic match. Illness occurred in only 1.9% of children in the FluMist™ group in 11.9% of children in the placebo group. The scope and severity of culture-confirmed influenza illness were similar in all children within the two years of the trial.

The Adult Effectiveness Study5,16

A multicenter, randomized, double-blind, placebo-controlled trial was conducted to evaluate the efficacy of FluMist™ in reducing influenza illness during a seven-week, site-specific peak outbreak period. The trial included 3,920 healthy adults aged 18 to 49 throughout the U.S. who were randomly selected to receive the vaccine or a placebo (in a ratio of 2:1).

Of all the subjects, 92.7% of the FluMist™ recipients and 93.0% of the placebo recipients were evaluated. The primary endpoint was the reduction in the number of subjects with one or more episodes of any febrile illness (AFI), characterized by the duration and extent of symptoms. Severe febrile illness (SFI) and febrile upper respiratory illness (FURI) were further defined and prospectively evaluated.

Overall, the vaccine brought about a 10.9% reduction (95% CI: −5.1, 24.4; P > .05) in patients with one or more episodes of AFI, a 19.5% decrease in SFI (95% CI: 3.0, 33.2; P ≤ .05), and a 23.7% reduction in FURI (95% CI: 6.7, 37.5; P ≤ .05). In the FluMist™ group, the AIs occurred at a rate of 13.73%; SFIs, at 10.37%; and FURIs, at 8.83%, respectively. In the placebo group, AIs occurred at a rate of 15.42%; SFIs, at 12.89%; and FURIs, at 11.58%, respectively.

The vaccine recipients did not experience a significant decrease in the number of AFI episodes, but significant reductions in SFIs and FURIs were observed.

The Challenge Study5,13

A multicenter, randomized, double-blind, placebo-controlled trial evaluated the efficacy of FluMist™ in preventing influenza after a challenge with wild-type virus in adults. This trial included 60 healthy adults, aged 18 to 41, who were serosusceptible to at least one strain of influenza included in the vaccine.

Twenty-nine adults were randomly assigned to a FluMist™ group, and 31 were assigned to a placebo group. Each subject was challenged with only one strain of wild-type virus that was specific to the individual’s serosusceptibility. Data were gathered, and the results included all three strains within each treatment group. Laboratory-confirmed influenza illness was found to be reduced by 85% (95% CI: 28, 100; P ≤ .05) in the vaccine group, compared with the placebo group.

Adverse Reactions

Prior to the approval and marketing of FluMist™, 20 clinical trials had been conducted to assess the safety of the vaccine. In all, approximately 28,000 doses of FluMist™ were administered to more than 20,000 subjects. A subset of these trials comprised randomized, placebo-controlled studies in which more than 4,000 healthy children, aged five to 17 years, and more than 2,000 healthy adults, aged 18 to 49, were vaccinated and evaluated. It was determined that the adverse drug effects that might have possibly complicated influenza (i.e., pneumonia, bronchitis, bronchiolitis, or central nervous system events) were not

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Who Should Not Receive FluMist™?</th>
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<tbody>
<tr>
<td>1. Children under the age of five and adults 50 years of age or older</td>
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<td>2. Patients with asthma, reactive airways disease, or other chronic disorders of the pulmonary or cardiovascular system</td>
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<td>3. Patients with other underlying medical conditions, specifically metabolic disease</td>
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<td>4. People with known or suspected immunodeficiency diseases or those who are receiving immunosuppressive therapies</td>
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<td>5. Children or adolescents who are receiving aspirin or other salicylates</td>
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<td>6. People with a history of Guillain-Barré syndrome</td>
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<td>7. Pregnant women</td>
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<tr>
<td>8. People with a history of hypersensitivity, including anaphylaxis, to any components of the vaccine or to eggs</td>
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Table 2 Vaccination Schedule for Children and Adults

<table>
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<tr>
<th>Age Group</th>
<th>Status</th>
<th>Dosage*</th>
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<tbody>
<tr>
<td>Children, five to eight years</td>
<td>Not previously vaccinated with FluMist™</td>
<td>Two doses (0.5 ml each, 60 days apart ± 14 days) for the initial season</td>
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<tr>
<td>Children, five to eight years</td>
<td>Previously vaccinated with FluMist™</td>
<td>One dose (0.5 ml) per season</td>
</tr>
<tr>
<td>Children and adults, nine to 49 years of age</td>
<td>Not applicable</td>
<td>One dose (0.5 ml) per season</td>
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</table>

* Each 0.5-ml dose of the vaccine should be administered as 0.25 ml in each nostril.


The most commonly reported signs and symptoms among children (aged five to 17 years) who received vaccination, as opposed to those who received placebo, included runny nose or nasal congestion, headache, fever, vomiting, abdominal pain, and myalgias. Many of these symptoms were associated more often with the first dose of the vaccine and were usually self-limited.

In one study, children from age one to 17 years were vaccinated and assessed. Unpublished data indicated an increase in asthma or reactive airways disease in the subset of patients who were one to five years of age within 42 days of vaccination, compared with the rates for placebo recipients. For this reason, FluMist™ was not approved for use in children younger than five years of age.

In the adult population studied (ages 18 to 49), runny nose or nasal congestion, headache, sore throat, cough, chills, and fatigue were more often reported among vaccine recipients than among placebo recipients. These symptoms were usually observed within seven days of each dosage administered.

**DRUG INTERACTIONS**

Children and adolescents receiving aspirin therapy or aspirin-containing products should not receive FluMist™ because of the increased association with Reye syndrome and wild-type influenza infection.

Although the concurrent use of FluMist™ with other antiviral compounds has not been evaluated, there is the potential for interference between these compounds. As a result, it is recommended that FluMist™ not be administered within 48 hours after antiviral therapy is discontinued. Antiviral agents should not be administered within two weeks of vaccination unless it is considered medically necessary.

Because the safety and immunogenicity of this vaccine and other concurrently administered vaccines have not been determined, FluMist™ should not be administered along with other vaccines. Intervals of two to four weeks between live virus and inactivated virus vaccinations are recommended.

**CONTRAINDICATIONS**

There are several contraindications for the use of FluMist™:
1. Under no circumstances should the vaccine be administered parenterally.
2. Individuals with a history of hypersensitivity—especially anaphylactic reactions—to any component of FluMist™, including eggs or egg products, should not receive this vaccine.
3. FluMist™ should not be given to children (ages five to 17) who are receiving aspirin or aspirin-containing therapy.
4. People with a history of Guillain-Barré syndrome should not receive the vaccine.
5. As with other live vaccines, FluMist™ should not be administered to individuals with known or suspected immune deficiency diseases (e.g., combined immunodeficiency, agammaglobulinemia, and thymic abnormalities or conditions such as human immunodeficiency virus infection, malignancy, leukemia, or lymphoma).

6. FluMist™ should not be given to patients with immunosuppression or altered or compromised immune status as a consequence of treatment with systemic corticosteroids, alkylating drugs, antimetabolites, radiation, or other immunosuppressive therapies.

**WARNINGS AND PRECAUTIONS**

Health care providers should consider the following facts before administering FluMist™:
1. The safety of FluMist™ in individuals with asthma or reactive airways disease has not been established.
2. 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 confirmed.
3. As with any vaccine, FluMist™ might not protect 100% of individuals receiving the vaccine.
4. FluMist™ recipients should avoid close contact with immunocompromised individuals (i.e., within the same household) for at least 21 days.
5. An epinephrine injection (1:1,000) or comparable treatment must be readily available in the event of an acute anaphylactic reaction following vaccination.
6. Vaccination should be postponed until after the acute phase (at least 72 hours) of a febrile or a respiratory illness.

**DOSE AND ADMINISTRATION**

FluMist™ should be administered according to the schedule shown in Table 2. Instructions are presented in Table 3.

**CONCLUSION**

Influenza remains a major concern worldwide. Vaccination is the most effective method of preventing illness caused by influenza. FluMist™, the first live, attenuated, intranasally adminis-

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5. FluMist™ (package insert, circular).

REFERENCES


5. FluMist™ (package insert, circular). Gaithersburg, MD: MedImmune; June 2003.5

Table 3 Instructions for Administration of Live, Attenuated Vaccine (FluMist™)

1. Thaw FluMist™ immediately before administration by holding the sprayer in the palm of the hand. Support the plunger rod with the thumb. Do not roll the sprayer or depress the plunger.

2. Remove the rubber tip protector.

3. While the patient is in an upright position with the head tilted back, place the rubber tip just inside the nostril to ensure that the product is delivered into the nose. Depress the plunger.

4. Pinch the nose, and remove the dose–divider clip from the plunger.

5. Place the tip just inside the other nostril. Depress the plunger to deliver the remaining vaccine.

Data from FluMist™ (package insert). Gaithersburg, MD: MedImmune; June 2003.5

* Store FluMist™ at 5°F (–15°C) or below until it is ready for use. Use freezers that are not frost-free to prevent temperature cycling above 5°F (–15°C), which may cause instability of the vaccine. FluMist™ may be thawed in a refrigerator for no more than 24 hours before use at 36°–46°F (2°–8°C).


Disclosure

Dr. Hilas and Dr. Marzella have no commercial or industrial relationships to disclose in regard to this article.