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REVIEW ARTICLE

Influenza Vaccination for the Pediatric Patient: A Focus on the New Intranasal, Cold-Adapted, Live Attenuated Vaccine

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FluMist is the first live attenuated, cold-adapted intranasal influenza vaccine (LAIV) approved for the prevention of influenza A and B. Clinical trials have shown that annual vaccination with LAIV is effective for the prevention of influenza. LAIV appears well tolerated in healthy patients 5–49 years of age. The most common adverse events are abdominal pain, chills, cough, diarrhea, headache, irritability, lethargy, muscle aches, otitis media, rhinitis, sinusitis, sore throat, and vomiting. FluMist has a novel intranasal route of administration that allows for influenza prevention without a painful intramuscular injection. Barriers preventing acceptance of LAIV include defining the appropriate patient population, cost, and insurance coverage.

Keywords: FluMist, Fluvirin, Fluzone, influenza, intranasal, vaccine

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INTRODUCTION

Influenza affects approximately 100,000 people in the United States each year.[1,2] Children have the highest incidence of influenza and are more likely to transmit the infection than adults.[3-5] Furthermore, infants require hospitalization due to influenza as often as the elderly.[3,4] Although rare, serious influenza infections also occur in healthy children who have little or no risk factors.[6] During the 2003–2004 influenza season, some children who contracted influenza developed severe sequelae such as encephalopathy, seizures, secondary bacterial pneumonia and death.[7] In addition to causing high morbidity and mortality the average cost for hospitalization due to influenza-related illness may be as high as $2108.[8] Even in low risk individuals, influenza often results in missed school days, doctor's office visits, and missed work by the child's parents.[3,9]

VACCINATION RECOMMENDATIONS

Currently, the Centers for Disease Control (CDC)/Advisory Committee on Immunization Practices (ACIP) guidelines recommend that infants 6 to 23 months of age , those in close contact with an infant between 0 and 23 months of age or any individuals at high risk of influenza complications should receive the inactivated intramuscular influenza vaccination (IMIV).[2] The CDC/ACIP encourages that all children 6 to 23 months of age be vaccinated with the split-virus IMIV.[2] They also recommend that anyone greater than 23 months of age who takes aspirin or those with chronic heart or lung disease should also be

ABBREVIATIONS: ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control; HAI, hemagglutination inhibition assay; HIV, Human Immunodeficiency Virus; IMIV, inactivated intramuscular influenza vaccination; LAIV, live attenuated intranasal vaccine

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Chiron has temporarily suspended manufacturing of Fluvirin (R) influenza virus vaccine; hence, the vaccine will not be released during the 2004-2005 influenza season.

vaccinated with an age-appropriate IMIV.[2] Children that would be considered at higher risk for influenza complications include those that have required medical attention in the prior year due to a chronic disease.[2] Chronic diseases include asthma, cardiac disease, chronic pulmonary disease, chronic renal dysfunction, cystic fibrosis, human immunodeficiency virus (HIV), immunosuppressive disease, metabolic disease and sickle cell anemia.[1,10]

AVAILABLE VACCINES

Three influenza vaccines are available currently in the United States. Both the IMIV and intranasal live attenuated, cold-adapted influenza virus vaccine (LAIV) were available for the first time in 2003.[1] The reassortant strains contained in all of the vaccines for the 2004–2005 season are A/Fujian/411/2002 (H3N2), A/New Caledonia/20/99 (H1N1), and B/Shanghai/361/2002.[2]

The inactivated intramuscular influenza vaccines

Vaccines for intramuscular administration are either split-virus or surface antigen. The split-virus vaccine Fluzone (Aventis Pasteur Inc., Swiftwater, PA) is approved for infants and children who are older than six months of age.[2,10] A split-virus vaccine may cause less injection reactions and febrile episodes when compared to the surface antigen vaccine.[11] However, this vaccine may provide slightly less immunogenicity than a surface antigen vaccine.[11] The surface antigen vaccine, Fluvirin (Chiron, Emeryville, CA) is only approved for those greater than 4 years of age.[2,10] Both vaccines are available in a preservative-free dosage form containing less than 1 mg of thimerosal per dose. They are also marketed as a standard thimerosal content form containing 25 mg thimerosal per dose.[2]

The preservative-free surface antigen vaccine is available as 0.5 mL single dose packages for children at least 48 months old. The split-virus vaccine is provided in preservative-free 0.25 mL unit dose syringes and 0.5 mL syringes that contain preservative. The 0.25 mL split-virus vaccine is marketed for children 6–35 months of age. The CDC/ACIP recommends that children should receive the inactivated influenza vaccine whether or not it contains standard or reduced thimerosal content because the theoretical mercury exposure risk is much less than the influenza risk.[2] Dosing of the IMIV is summarized in Table 1.

Table 1. The ACIP Dosage Schedule for the intramuscular influenza vaccine

Age	Dose (mL)	Number of Doses
6–35 mo	0.25	1 or 2
3–8 yrs	0.5	1 or 2
$\geq$ 9 yrs	0.5	1

Table 1 is modified from reference 2.

The intranasal live attenuated influenza vaccine

FluMist, a trivalent LAIV, received Food and Drug Administration approval on June 17, 2003.[1] The vaccine provides active immunization against disease caused by influenza A or B and is approved for use in healthy children, adolescents, and adults 5 to 49 years of age.[12] It is comprised of the same 3 antigen strains (2 influenza A and 1 influenza B) as contained in the IMIV. The viruses that make up the LAIV vaccine, like the IMIV, demonstrate the phenotypic properties of influenza types A and B from the Master Donor Virus and express the hemagglutinin and neuraminidase surface glycoproteins recommended by the Public Health Service.[1] Immunity against the glycoprotein limits the extent of disease if infection occurs.[1]

The adverse events associated with the attenuated vaccine are coryza, headache, and muscle aches. Since LAIV is a cold-adapted virus, it will not replicate well at temperatures greater than 25°C.[13] A cold-adapted virus will not replicate well in the lungs, but will reproduce in the nasopharynx, thereby facilitating an immune response to influenza at the site of entry.[13] The majority of children studied shed at least one of the three vaccine viruses. Patients immunized with LAIV, a live virus vaccine, may shed the virus for up to 3 weeks (mean duration 6.2 $\pm$ 4.6 days) and transmission via shedding vaccine virus has been demonstrated.[14]

PEDIATRIC CLINICAL TRIALS

Approximately 10,000 patients between the ages of 5 and 17 years received at least one dose of a LAIV in clinical trials.[15-21] To date, seven trials have been published (Tables 2, 3). Neuzil et al. compared the efficacy of a cold-adapted bivalent intranasal influenza vaccine to a vaccine against inactivated intramuscular bivalent influenza A or placebo.[16] The study was conducted over a five-

Table 2. Summary of efficacy studies using the live attenuated influenza vaccine in children

	References 16 & 17	Reference 19
Patients	791 healthy children; Age: 1–16 years	1602 healthy children; Age: 15–71 months
Exclusion Criteria	Egg allergy, chronic disease, pregnant, taking corticosteroids or immunosuppressants	Egg allergy, chronic illness
Efficacy	**LAIV* vs. IMIV** H1N1‡ LAIV 95% (CI_{95} 67–99) vs. IMIV 91% (CI_{95} 64–98) H3N2 LAIV 68% (CI_{95} 1–90) vs. IMIV 77% (CI_{95} 20–93)	**LAIV vs. placebo:** One dose/two doses LAIV† Influenza A H3N2‡ 87%(CI_{95} 47–97)/ 96% (CI_{95} 90–99) Influenza B 91%(CI_{95} 46–99)/91% (CI_{95} 78–96) Efficacy after 2 years to H1N1 vaccine virus challenge 86% (CI_{95} 60-93)

**influenza A not B*
†Patients received 1 or 2 doses based on study center
‡H-hemagglutinin & N-neuraminidase surface glycoproteins

year period and children were randomized to receive one dose of vaccine or placebo each year. Immunogenicity was determined by a hemagglutination inhibition assay (HAI). Although children less than six years old who were originally seronegative demonstrated an immunologic response, the response appeared more pronounced in children greater than 6-years-old. Furthermore, the LAIV was more likely to produce an immunogenic response against H1N1 than H3N2.

In a Phase III randomized double-blind placebo-controlled study, a trivalent LAIV was evaluated to determine if it was better than placebo at preventing culture confirmed influenza.[19] Two does of the vaccine were given to 1314 children while 288 children received only one dose. Two hundred and three children were evaluated for immunogenicity using HAI. Efficacy was determined by influenza rates. One dose of the vaccine demonstrated immunogenicity against influenza A H3N2 and influenza B. Two doses were required to produce significant immunogenicity against influenza A H1N1. Greater than 90% of the time the LAIV prevented influenza. Furthermore, subjects who received the LAIV had less febrile illness ($P < 0.001$) and less acute otitis media ($P < 0.001$) during the study.

After the second year of the study, and six to eight months after the last vaccination, children were challenged with the H1N1 vaccine virus.[20] The LAIV was more likely than placebo to prevent viral shedding. When vaccine virus shedding occurred it usually happened on day two or three. Viral shedding stopped more quickly in those who received the LAIV as compared to the placebo group ($P = 0.001$). Immunogenicity was evaluated by both HAI and nasal IgA antibody concentrations. Influenza prevention correlated with both the presence of HAI serum antibody and nasal IgA antibody.

To date, only small studies have been conducted in high-risk children with asthma[21] and Human Immunodeficiency Virus (HIV) infection.[22] Forty-eight asthmatic children were randomized 1:1 to receive either LAIV or placebo.[21] Children receiving LAIV had a higher incidence of asthma exacerbations; however, the difference was not statistically significant. A recent study compared the safety and efficacy of LAIV in 25 HIV positive children to 24 HIV negative children.[21] According to the CDC clinical and immunologic classification none of the HIV positive children were severely immunocompromised. After two doses of LAIV, an immune response to at least one strain of the virus was demonstrated in 88% (CI_{95} 47–100) of HIV-infected and 100% (CI_{95} 84–100) of the non-HIV-infected children. Two HIV-infected patients (0 non-infected) reported an upper respiratory tract infection. The HIV viral load, CD4+ T-cell counts and percentages remained stable for 4–5 months post-vaccination. Furthermore, LAIV nasal shedding was similar in HIV-infected and non-infected children. At this point there is not enough information to recommend the LAIV in either of these populations. FDA approved FluMist for healthy individuals 5–49 years of age since safety and efficacy data for patients with chronic disease including asthma is lacking.[12]

At this time there are many contraindications to the LAIV, which include patients with a history of hypersensitivity to eggs or egg products, children or adolescents taking aspirin or aspirin-containing therapy, children with a history of Guillain-Barre syndrome, and those < 5 years of age. Ad-

Table 3. Summary of safety studies using the live attenuated influenza vaccine in children

	Reference 15	Reference 21
Patients	6743 healthy children (1–17 years)	48 Asthmatic children (9–17 years)
Exclusion Criteria	Recent vaccination; egg allergy; asthma; fever; immunodeficiency; respiratory illness; immunosuppressants	Egg allergy; intranasal corticosteroid; antiviral medication; febrile illness
Safety	LAIV vs. placebo	LAIV vs. placebo
	No difference in overall incidence of medically evaluated adverse events 0.2% (both groups)	Peak expiratory flow rate $\geq$ 15% or $\geq$ 2 SD worse than baseline (P = 0.06)
	18–35 mo: increased incidence in 42 days after vaccination of: Asthma (RR = 4.06 CI_{90} 1.29–17.86), Upper respiratory infection (RR = 1.32 CI_{90} 1.30–1.67)	LAIV higher incidence of asthma exacerbations (8% vs. 0%*)

**non-significant*

ditionally, LAIV should be avoided until the safety can be established in patients with chronic medical conditions.[12] Underlying medical conditions defined by the ACIP include chronic cardiovascular, pulmonary and metabolic diseases, renal dysfunction, hemoglobinopathies and congenital or acquired immunosuppression (i.e., HIV, malignancy, corticosteroids, alkylating agents, antimetabolites, radiation or any other immunosuppressant).[1] To prevent viral transmission the ACIP also recommends that individuals should not be vaccinated with LAIV if they will be in close contact with severely immunosuppressed patients within seven days of vaccination.[1,2]

Recommended dosing for LAIV is summarized in Table 4. Those who require two doses of the vaccine are not required to receive the same type vaccine for both doses. When giving one dose of LAIV and one dose of IMIV, the time between vaccines should be determined by the type of vaccine that was given first.[23]

ADVERSE EFFECTS AND DRUG-INTERACTIONS

LAIV appears to be well tolerated in most age groups. Recently, the safety of LAIV in 6743 children and adolescents was reported.[15] The LAIV or placebo was administered in a double blind manner to children 1–17 years of age. Children < 9-years-old received a second dose 28 to 42 days following the first. Safety was evaluated for 42 days following administration of the dose. The incidence of adverse events requiring medical attention was similar between the active and placebo groups. In a subgroup analysis, vaccinated children 12–35 months of age had an increased risk of asthma (RR 4.06: CI_{90} 1.29–17.86) and upper respiratory infection (RR 1.32: CI_{90} 1.30–1.67) versus controls.[15] A cumulative age analysis of this data showed that children 12–59 months appeared to have an increased risk of asthma or reactive airway disease after the first vaccine dose (RR 3.53: CI_{90} 1.1–15.7).[14]

The most common adverse events reported in clinical trials were abdominal pain, chills, cough, diarrhea, headache, irritability, lethargy, muscle aches, nasal congestion, otitis media, runny nose, sinusitis, sore throat, and vomiting. Like other live virus vaccines, LAIV can be given concurrently with other vaccines.[23] Inactivated vaccines can be given either before or after the LAIV. If live virus vaccines, such as varicella, rubella, measles, mumps, oral poliovirus, or yellow fever are not given together, they should be separated by one month.[23] Suspected drug-drug interactions include aspirin, immunosuppressants, and antivirals.

VACCINE COST

The cost of the LAIV for the 2004–2005 year is estimated to be between $1–23.50 per dose,[24] while the IMIV vaccine is only $5 to $10. Initially insurance companies were not providing reimbursement for LAIV, however each day this barrier is being overcome. Currently the Federal Vaccines for Children Program is only funding the inactivated influenza vaccinations (IMIV) for infants and children 6 to 23 months of age and older children who live with infants and children 6- to 23-months-old.

SUMMARY

The LAIV has a small but definitive place in therapy. Intranasal administration of a live virus

Table 4. Intranasal live attenuated vaccine dosage schedule[1]

Age (yrs)	Vaccination Status	Dosage Schedule
≥ 5–8	First vaccination with LAIV	2 doses (0.5 mL each, 60 ± 14 days apart)
≥ 5–8	Previous vaccination with LAIV	1 dose (0.5 mL) annually
≥ 9-49	History not required	1 dose (0.5 mL) annually

The 0.5 mL dose is 0.25 mL in each nostril

vaccine appears to have similar or better efficacy than an IMIV.[17] Because LAIV is a live virus it may have a longer duration of efficacy.[20] Furthermore, the intranasal route of administration would be preferred by many children and their parents over an intramuscular injection. The CDC recommendations regarding LAIV are consistent with FDA approved pediatric indications for healthy children older than five years of age. The LAIV is a convenient way to administer the influenza vaccine although the high cost may be a deterrent to children without adequate insurance coverage. Many young children will have the opportunity to receive the IMIV at no cost while some insurance companies and the Vaccines for Children program will currently not reimburse for the LAIV. As a result of recent severe influenza cases, FluMist may potentially be used in the future to vaccinate more school-aged children. To date, FluMist has been shown to provide at least equivalent efficacy to the IMIV. Further research is needed to evaluate safety in all populations, especially young children.

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REFERENCES

1. Harper SA, Fukuda K, Cox NJ, Bridges CB; Advisory Committee on Immunization Practices. Using live, attenuated influenza vaccine for prevention and control of influenza: supplemental recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2003;52:1-8.
2. Harper SA, Fukuda K, Uyeki TM, Cox NJ, Bridges CB; Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP). Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2004;53:1-40.
3. Neuzil KM, Mellen BG, Wright PF, Mitchel EF Jr, Griffin MR. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. N Engl J Med 2000;342:225-31.
4. Izurieta HS, Thompson WW, Kramarz P, Shay DK, Davis RL, DeStefano F, et al. Influenza and the rates of hospitalizations for respiratory disease among infants and young children. N Engl J Med 2000;342:232-9.
5. Jacobson RM, Poland GA. Universal vaccination of healthy children against influenza. Pediatr Drugs 2002;4:65-71.
6. Centers for Disease Control and Prevention. Severe morbidity and mortality associated with influenza in children and young adults—Michigan, 2003. MMWR Morb Mortal Wkly Rep. 2003;52:837-40.
7. Centers for Disease Control and Prevention. Update: Influenza activity—United States, 2003–04 Season. MMWR Morb Mortal Wkly Rep. 2003;52:1197-1202.
8. Luce BR, Zangwill KM, Palmer CS, Mendelman PM, Yan L, Wolff MC, et al. Cost-effectiveness analysis of an intranasal influenza vaccine for the prevention of influenza in healthy children. Pediatrics 2001;108:E24.
9. Nichol KL, Lind A, Margolis KL. The effectiveness of vaccination against influenza in healthy, working adults. N Engl J Med 1995;333:889-93.
10. American Academy of Pediatrics. Influenza. In: Pickering LK, ed. Red Book: 2003 Report of the Committee on Infectious Diseases. 26th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2003:388.
11. Squarcione S, Sgricia S, Biasio LR, Perinetti E. Comparison of the reactogenicity and immunogenicity of a split and a subunit-adjuvanted influenza vaccine in elderly subjects. Vaccine 2003;21:1268-74.
12. FluMist® Package Insert. Gaithersburg, MD: Medimmune Vaccines, Inc, June 16, 2003.

13. Edwards KM, King JC, Steinhoff MC, Thompson J, Clements ML, Wright PF, et al. Safety and immunogenicity of live attenuated cold-adapted influenza B/Ann Arbor/1/86 reassortant virus vaccine in infants and children. J Infect Dis 1991;163:740-5.
14. FDA Clinical Briefing Document for MedImmune Vaccines Inc. Cold-adapted influenza vaccine, trivalent - FluMist™. Available at www.fda.gov/ohrms/dockets/ac/02/briefing/3912B1_01.doc Accessed December 04, 2003.
15. Bergen R, Black S, Shinefield H, Lewis E, Ray P, Hansen J, et al. Safety of cold-adapted live attenuated influenza vaccine in a large cohort of children and adolescents. Pediatr Infect Dis J. 2004;23:138-44.
16. Neuzil KM, Dupont WD, Wright PF, Edwards KM. Efficacy of inactivated and cold-adapted vaccines against influenza A infection, 1985 to 1990: the pediatric experience. Pediatr Infect Dis J 2001;20:733-40.
17. Edwards KM, Dupont WD, Westrich MK, Plummer WD Jr., Palmer PS, Wright PF. A randomized controlled trial of cold-adapted and inactivated vaccines for the prevention of influenza A disease. J Infect Dis 1994;169:68-76.
18. Piedra PA, Yan L, Kotloff K, Zangwill K, Bernstein DI, King J, et al. Safety of the trivalent, cold-adapted influenza vaccine in preschool-aged children. Pediatrics 2002;110:662-72.
19. Belshe RB, Mendelman PM, Treanor J, King J, Gruber WC, Piedra P, et al. The efficacy of live attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine in children. N Engl J Med 1998;338:1405-12.
20. Belshe RB, Gruber WC, Mendelman PM, Mehta HB, Mahmood K, Reisinger K, et al. Correlates of immune protection induced by live, attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine. J Infect Dis 2000;181:1133-7.
21. Redding G, Walker RE, Hessel C, Virant FS, Ayars GH, Bensch G, et al. Safety and tolerability of cold-adapted influenza vaccine in children and adolescents with asthma. Pediatr Infect Dis J 2002;21:44-8.
22. King JC Jr, Fast PE, Zangwill KM, Weinberg GA, Wolff M, Yan L, et al. Safety, vaccine virus shedding and immunogenicity of trivalent, cold-adapted, live attenuated influenza vaccine administered to human immunodeficiency virus-infected and noninfected children. Pediatr Infect Dis J 2001;20:1124-31.
23. Centers for Disease Control and Prevention: National Center for Infectious Diseases, Questions & Answers about FluMist®. Available at www.cdc.gov/ncidod/diseases/flu/laiv.html. Accessed October 29, 2003.
24. Personal Communication: Medimmune Vaccines, Inc, July 1, 2004. Gaithersburg, MD.