



Release Date: October 2006

Valid Until: December 2006

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Learning Objectives

After studying the literature presented in this Pediatric Respiratory Care series, participants will be able to:

- Identify respiratory disorders in pediatric patients
- Summarize risk factors for respiratory disorders in pediatric patients
- Select an appropriate therapeutic regimen for patients with pediatric respiratory disorders

Target Audience

This educational activity is designed for pediatricians, primary care physicians, pediatric and family nurse practitioners, neonatologists, infectious disease specialists, allergists, pulmonologists, immunologists, and other healthcare professionals involved in the care and management of pediatric respiratory patients.

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This CME activity is supported by an educational grant from MedImmune, Inc.

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Low Transmissibility of Cold-Adapted Influenza Vaccine Viruses in Day-Care Children

The live attenuated influenza vaccine (LAIV) is a nasal vaccine containing three cold-adapted influenza vaccine viruses.

Approved by the U.S. Food and Drug Administration in 2003, the LAIV is currently indicated for the prevention of influenza in healthy individuals 5 to 49 years of age. Although transmission of vaccine virus is a concern, studies with LAIV have not detected postvaccination transmission to close contacts.

Recently, Vesikari and colleagues estimated the probability of postvaccination transmission between young day-care children in a prospective, randomized, double-blind study. A total of 197 healthy children, 9 to 36 months of age, attending day care were assigned to receive intranasal LAIV (n=98) or placebo (n=99). Postvaccination viral shedding, transmission probability, genotype and phenotype of shed viruses, and safety were evaluated.

Completion rates were high, with 98% of the vaccine recipients and 96% of placebo recipients completing the study. Among 98 vaccine recipients during the 3-week postvaccination period, 80% shed at least one vaccine strain, 44% shed type A vaccine virus, 74% shed type B vaccine virus, 38% shed both type A and B strains, and 6% shed all three vaccine strains. The A/H3N2 vaccine strain was shed for the longest time period, followed by the B strain and the

A/H1N1 strain. Furthermore, a greater proportion of subjects shed type B strain each day than either type A/H1N1 or type A/H3N2 strains.

One confirmed transmission of a vaccine virus (type B) to a single placebo recipient was identified. The transmitted virus did not cause clinically significant illness in this individual. Assuming a single confirmed transmission event, the estimated transmission rate, based on the Greenwood model, was 1.01% (one of 99). The Reed-Frost model analysis was performed on data from the 93 placebo recipients enrolled in the study who were in a contact group/playroom with at least one LAIV-vaccinated child. Assuming a single confirmed transmission event, the calculated probability of transmission of a vaccine virus to a child in a contact group with a single vaccinated child was 0.58% (95% confidence interval [CI], 0%–1.72%). Transmission probabilities for groups with 2, 3, 4, or 5 vaccinated children were 1.16%, 1.73%, 2.3%, and 2.87%, respectively.

Isolates of vaccine virus maintained their phenotypic characteristics (cold adaptation and temperature sensitivity) and did not revert at nucleotides conferring an attenuating phenotype. The *cs* and *ts* phenotypes were preserved in all of the shed vaccine viruses tested, including the type B vaccine virus strain isolated from the single placebo recipient.

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Disclosures:

- * Dr Piedra is professor of molecular virology and microbiology, and pediatrics at Baylor College of Medicine. He has indicated relevant financial relationships as noted: he receives grant/research support from MedImmune, Inc.; is a speaker for MedImmune, Inc.; is an expert witness for Sanofi-Pasteur; and is an ad hoc consultant for GlaxoSmithKline, MedImmune, Inc., and Sanofi-Pasteur.
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Low Transmissibility of Cold-Adapted Influenza (Continued)

There were no statistically significant differences between the LAIV and placebo groups in solicited adverse events. The most frequently experienced solicited adverse events in the vaccine and placebo groups were rhinorrhea or nasal congestion (80.2% vs 75.3%; $P=0.49$), cough (50.5% vs 50.5%; $P>0.99$), fever $\geq 38^{\circ}\text{C}$ (51.2% vs 51.2%; $P>0.99$), and irritability (41.5% vs 33.7%; $P=0.30$). Clinically significant respiratory adverse events occurring within 21 days after vaccination occurred in a similar proportion of vaccine and placebo patients (14.3% vs 16.2%).

This study was the largest to date monitoring influenza transmission. These results indicated that young children in a day-care setting have a high rate of vaccine virus shedding, the

shed vaccine viruses are stable and do not revert to wild-type viruses, and there is a low rate of vaccine virus transmission in a setting designed to maximize the opportunity for transmission. The estimated risk of transmission and estimated probability of transmission were low. The study investigators stated that this low transmissibility is offset by potential significant reductions in wild-type influenza burden in young children receiving LAIV.

Vesikari T, Karvonen A, Korhonen T, et al. A randomized, double-blind study of the safety, transmissibility and phenotypic and genotypic stability of cold-adapted influenza virus vaccine. *Pediatr Infect Dis J*. 2006;25:590-595.

Note: LAIV is not indicated for use in persons younger than age 5 or older than age 49.

COMMENTARY

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Influenza immunization of young children is currently a topic of particular interest for several reasons: (1) The CDC has expanded their recommendations for annual influenza immunization to include all children 6 months to 5 years of age, and is considering the inclusion of older children; (2) This requires an adequate and increasing vaccine supply, especially if a pandemic or severe intraepidemic outbreak occurs; (3) Rapid production of trivalent inactivated vaccine (TIV) containing the predicted seasonal strain has often been problematic.

Potential solutions involve not only increasing the supply of vaccines, but also using vaccines with enhanced efficacy that do not require the annual immunization of large populations. The live-attenuated vaccine (LAIV) has been shown to provide better and longer lasting protection against both matched and mismatched strains as compared with TIV¹⁻⁵. Currently, LAIV is only approved for persons between 5 and 49 years of age. However, the highest rates of influenza hospitalizations occur in children younger than 5 years of age, especially infants. The necessary approval to use LAIV in infants and toddlers will depend on further studies of its safety and efficacy with this young age group. This and other studies by these authors, involving young children, including infants 6 to 24 weeks, are major steps toward this goal.^{2,6,7}

References:

¹Belshe R et al. *N Engl J Med*. 1998;338:1405; ²Ashkenazi S et al. PAS Abstract, May 2004; ³Piedra PA et al. *Pediatrics*. 2005;116:e397; ⁴Mendelman PM et al. *Pediatr Infect Dis J*. 2004;23:1053; ⁵Belshe R et al. *J Pediatr*. 2000;136:168; ⁶Vesikari T et al. PAS Abstract, May 2006; ⁷CAIV Study Group. PAS Abstract, May 2006.

Immunogenicity to Trivalent Inactivated Influenza Vaccine in Partially Immunized Toddlers

In most years, one or more of the virus components of the trivalent inactivated influenza vaccine (TIV) is changed to provide better protection against the new or drifted epidemic influenza virus. Current immunization guidelines recommend that children ≥ 6 months of age who have previously received one dose of TIV should be given a single dose the following fall. However, there is limited data documenting the immunogenicity of two doses of TIV that are of different formulations given in separate years to young children. In 2004, the TIV formulation had

been revised compared to the 2003 TIV vaccine. The 2004 TIV had changed the A/H3N2 (minor change) and B (major change) antigens, permitting assessment of the impact of antigenic changes on the single-dose recommendation in partially immunized toddlers.

Englund and associates performed an observational, nonrandomized, open-label study comparing the immunogenicity of two TIV doses in two groups of healthy children 6 to 23 months of age. In Group 1, children who had received one dose of 2003 TIV the previous season

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Study investigators recommend two doses of TIV to toddlers who have not been vaccinated previously, even when the vaccine is in short supply.

PRCI MISSION STATEMENT

The PRCI is a multicomponent educational program on pediatric respiratory disorders designed for pediatricians, primary care physicians, pediatric and family nurse practitioners, neonatologists, infectious disease specialists, allergists, pulmonologists, immunologists, and other healthcare professionals involved in the care and management of pediatric respiratory patients. PRCI programs address issues concerning asthma, respiratory syncytial virus, and other respiratory tract infections and disorders. Methods to prevent, control, and treat respiratory illnesses in children are also evaluated.

Immunogenicity to Trivalent Inactivated Influenza (Continued)

received one dose of 2004 TIV according to current guidelines. In Group 2, TIV-naïve toddlers received the standard two doses of 2004 TIV given 1 month apart. The primary outcome was antibody response to the H1N1, H3N2, and B antigens in the 2004 TIV at 4 weeks after the second dose, as determined by hemagglutination-inhibition antibody titers.

A total of 122 study participants were enrolled in this study. Fifty-six of 58 previously immunized children in Group 1, and 63 of 64 vaccine-naïve children in Group 2 completed the study. Antibody responses to the unchanged H1N1 antigen observed 4 weeks after the second TIV dose were similar in the two groups. Groups 1 and 2 had good responses to the H1N1 antigen as measured by geometric mean titer (75.2 vs 69.1) and percentage with antibody titers $\geq 1:32$ (82.1% vs 85.7%). For the changed H3N2 antigen, there was a significantly higher geometric mean titer in Group 1 compared with Group 2 (156 vs 53.7). However, with regard to the H3N2 antigen, both groups had very high rates of seroconversion that were not statistically different (91% vs 84%). The antibody response to a changed influenza B antigen was significantly lower in Group 1 than in Group 2, as measured by both geometric mean titer (13.8 vs 49.1) and percentage with antibody titers $\geq 1:32$ (27% vs

86%; $P < 0.001$). In general, non-inferiority of the antibody response for Group 1 compared with Group 2 was confirmed for the influenza A/H3N2 antigen ($P < 0.001$), was marginally significant for the influenza A/H1N1 antigen ($P = 0.054$), and was not confirmed for influenza B antigen.

In this study, partially immunized subjects demonstrated relatively good responses to the vaccine antigen with minor changes (H3N2 antigen) but weak responses to the vaccine antigen with major changes (B antigen). Based on these results, the study investigators recommend two doses of TIV to toddlers who have not been vaccinated previously, even when the vaccine is in short supply. These findings underscore the benefits of a second vaccine dose, whether this dose is identical or not identical to the original priming dose. Furthermore, these results support the current recommendation for using TIV in unimmunized and partially immunized young children. Limitations of this study included the lack of randomization and the lack of a control group.

Englund JA, Walter EB, Gbadebo A, et al. Immunization with trivalent inactivated influenza vaccine in partially immunized toddlers. *Pediatrics*. 2006;118:e579-e585.

Clinical Insights® in Pediatric Respiratory Care Post-test

1. Among young children in a day-care setting:
 - a. There is a high rate of LAIV virus shedding.
 - b. There is a low rate of LAIV virus shedding.
 - c. There is a low rate of LAIV virus transmission.
 - d. A and C
 - e. B and C
2. In this study, subjects receiving one dose of 2003 TIV the previous season and one dose of 2004 TIV demonstrated:
 - a. Relatively good responses to the vaccine antigen with minor changes between 2003 and 2004 (H3N2 antigen).
 - b. Weak responses to the vaccine antigen with major changes between 2003 and 2004 (B antigen).
 - c. Responses only to the vaccine antigen that was unchanged between 2003 and 2004 (H1N1 antigen).
 - d. A and B

1. d. This study indicated that young children in a day-care setting have a high rate of vaccine virus shedding but a low rate of vaccine virus transmission.
 2. d. In this study, partially immunized subjects demonstrated relatively good responses to the vaccine antigen with minor changes (H3N2 antigen) but weak responses to the vaccine antigen with major changes (B antigen).

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