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Learning Objectives

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

- Describe the benefits of using live attenuated trivalent influenza vaccine (LAIV) versus trivalent inactivated influenza vaccine (TIV) in young children and adults
- Assess the risks associated with LAIV administration in young children and delineate the population of children who are potential candidates for LAIV
- Recognize the differences in efficacy between TIV and LAIV against antigenically drifted influenza and influenza A and B virus strains

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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Comparison of the Live Attenuated and Inactivated Influenza Vaccines in Infants and Young Children

Currently, US advisory bodies recommend universal vaccination of children 6 to 59 months of age with trivalent inactivated influenza vaccine (TIV). Live attenuated trivalent influenza vaccine (LAIV) is not currently licensed for children younger than 5 years of age. Vaccination of young children is a daunting task given the limited supplies caused by vaccine shortage or delayed distribution during many influenza seasons, and the difficulty of adding another shot to a busy childhood vaccine schedule. The latest research suggests that LAIV, when licensed, might be an alternative vaccine approach to the prevention of influenza in young children.

In a multicenter study recently conducted in the United States, Europe, the Middle East, and Asia, Belshe and colleagues compared the safety and efficacy of LAIV with that of TIV in infants and young children. In that study, children 6 to 59 months of age, without a recent episode of wheezing illness or severe asthma, were randomly assigned in a 1:1 ratio to receive either LAIV or TIV. Throughout the 2004–2005 influenza season, influenza-like illness was monitored in study participants with cultures.

A total of 8,475 children were enrolled in the study, with 7,852 children completing the study according to the protocol. Over the influenza surveillance period, there were 54.9% fewer cases of cultured-confirmed influenza

in the LAIV group (153 cases; attack rate, 3.9%) than in the TIV group (338 cases; attack rate, 8.6%) ($P<0.001$). Vaccination with LAIV resulted in 89.2% fewer cases of influenza A/H1N1 ($P<0.001$), 79.2% fewer cases of influenza A/H3N2 ($P<0.001$), and 16.1% fewer cases of influenza B ($P=0.19$). LAIV was significantly more protective than TIV against both well-matched (influenza A/H1N1 attack rate reduction, 89.2%) and mismatched (influenza A/H3N2 attack rate reduction, 79.2%) influenza A viruses.

Safety data were available for 8,352 children in this study. Overall, there was no significant difference in medically significant wheezing between children receiving TIV and those receiving LAIV. However, a significant increase in wheezing with LAIV, compared with TIV, was noted after dose 1 primarily during the second, third, and fourth weeks after vaccination. The authors suggested that the wheezing was related to the peak of viral replication and immune responses to the viruses. The difference in wheezing occurred primarily in children younger than 12 months of age. Among previously unvaccinated children 6 to 11 months old, medically significant wheezing within 42 days after the administration of dose 1 was more common with LAIV (3.8%) than with TIV (2.1%) ($P=0.08$). Furthermore, among children 6 to 11 months of age, hospitalization rates for any cause during the 180 days after vaccination were higher

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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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Comparison of the Influenza Vaccines *(Continued)*

among the recipients of LAIV (6.1%) than among the recipients of TIV (2.6%) ($P=0.002$). The incidence of serious adverse events was similar for the 2 groups.

The authors conclude that the efficacy of LAIV is superior to that of TIV. Taking into account the safety data, LAIV should be a safe

and effective option for children 12 to 59 months of age who do not have a history of asthma or wheezing.

Belshe RB, Edwards KM, Vesikari T, et al. Live attenuated versus inactivated influenza vaccine in infants and young children. *N Engl J Med*. 2007;356:685-696.

COMMENTARY

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Influenza vaccination of children has become an important concept, perhaps mostly because vaccination of children (who generally develop comparatively milder influenza-related illness) may be the best way to protect the elderly against life-threatening influenza infection. Live influenza vaccines may be more effective in young children than inactivated vaccines, especially when the circulating strain does not match the vaccine strain well; the situation may be reversed in adults. Live vaccines may be more effective in those with less lifetime exposure to influenza, or the mechanism of protection may be different in children. An important issue to resolve is the possible lower efficacy of live vaccines against type B influenza. The transient increase in wheezing after live vaccination in children must be balanced against greater protection against influenza. These episodes, apparently mild in nature, may occur as a result of live virus entering the airway of children already predisposed to airway obstruction.

Efficacy of Inactivated and Live Attenuated Vaccines for Drifted Influenza Strains

In February of each year, influenza virus strains for the next season's vaccine are selected. Usually, the next influenza outbreak is caused by a virus or viruses similar or to identical to those in the vaccine. However, the efficacy of influenza vaccines may diminish during seasons when the circulating viruses have antigenically drifted from the vaccine viruses.

During the 2004–2005 influenza season in Michigan, Ohmit and associates conducted a study to determine the efficacy of both the trivalent inactivated influenza vaccine (TIV) and the live attenuated trivalent influenza vaccine (LAIV) in healthy adults 18 to 46 years of age, for whom both vaccines are approved for use. A study enrollment of 1,800 subjects was estimated to be necessary for demonstrating vaccine efficacy with an attack rate of 5% and 80% vaccine efficacy. A total of 1,247 persons (mean age, 26.9 years) were randomized to receive TIV ($n=519$), LAIV ($n=522$), or placebo ($n=206$) between October and December 2004. In this study, influenza activity began in January 2005 with the circulation of an antigenically drifted type A (H3N2) virus, the A/California/07/2004-like strain, and with the co-circulation of 2 lineages of type B viruses.

In general both vaccines were well tolerated. TIV recipients were significantly more likely to report runny nose/congestion (29.9%

vs 20.2%; $P=0.05$) and arm soreness (53.9% vs 20.2%; $P<0.001$) compared to the intramuscular injection placebo group. LAIV recipients were more likely to report runny nose/congestion (48.8% vs 30.3%; $P=0.001$), cough (18.2% vs 8.1%; $P=0.01$), headache (37.9% vs 25.3%; $P=0.02$), and muscle ache (13.2% vs 5.1%; $P<0.02$) than were the intranasal spray placebo recipients. Of note, the proportions of subjects in the intramuscular injection placebo group with cough (16.2%) and muscle aches (13.1%) were similar to those of the LAIV recipients.

Absolute vaccine efficacy (compared with placebo), as estimated for culture-confirmed cases only, was 77% (95% confidence interval [CI], 37 to 92) for TIV and 57% (95% CI, -3 to 82) for LAIV. There was a 46% relative reduction (95% CI, -44 to 82) that was not significant in culture-confirmed influenza among those receiving TIV versus those receiving LAIV. Absolute vaccine efficacy, as measured by either isolating the virus in cell culture or identifying it through real-time polymerase chain reaction (PCR), was 75% (95% CI, 42 to 90) for TIV and 48% (95% CI, -7 to 74) for LAIV. There was a 53% relative reduction (95% CI, -5 to 80) that was not significant among those receiving TIV versus those receiving LAIV. Absolute vaccine efficacy, as measured by either isolating the virus or

During the 2004-2005 influenza season, in which most circulating viruses were antigenically drifted, TIV and LAIV prevented influenza A infections equally well.

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Efficacy of Inactivated and Live Attenuated Vaccines *(Continued)*

observing a rise in the serum antibody titer, was 67% (95% CI, 16 to 87) for TIV and 30% (95% CI, -57 to 67) for LAIV. There was a 53% relative reduction (95% CI, -4 to 80) in these cases that was not significant among those receiving TIV versus those receiving LAIV. The use of antibody titers to confirm influenza infection is likely to underestimate infections in TIV recipients, which will impact on its true efficacy.

Vaccine efficacy was comparable between the two vaccines against influenza type A infection. Absolute vaccine efficacy against culture-confirmed influenza A was 74% (4 cases; attack rate 0.8%; 95% CI, -11 to 95) for TIV and 74% (4 cases; attack rate 0.8% 95% CI, -12 to 95) for LAIV. Considering only type B viruses, the absolute efficacy against culture-confirmed illness was 80% (3 cases; attack rate 0.6%; 95% CI, 8 to 97) for TIV and 40% (9 cases; attack rate 1.7%; 95% CI,

-103 to 81) for LAIV. The attack rate for culture positive infection in the placebo group was 2.9% (6 cases) for influenza A and 2.9% (6 cases) for influenza B.

During the 2004–2005 influenza season, in which most circulating viruses were antigenically drifted, TIV and LAIV prevented influenza A infections equally well. TIV prevented more cases of laboratory-confirmed influenza B infections compared to LAIV. A major limitation of this study was that it was underpowered and coupled with the low attack rate it becomes difficult to interpret the relative efficacy of these vaccines. Additional studies in adults are needed with adequate sample size to determine their relative performance.

Ohmit SE, Victor JC, Rotthoff JR, et al. Prevention of antigenically drifted influenza by inactivated and live attenuated vaccines. *N Engl J Med*. 2006;355:2513-2522.

Clinical Insights® in Pediatric Respiratory Care Post-Test

1. Regarding the results of the study comparing LAIV and TIV in children, which of the following statements is false?
 - a. LAIV was associated with fewer cases of cultured-confirmed influenza than TIV.
 - b. LAIV was significantly more protective than TIV against well-matched but not mismatched influenza A viruses.
 - c. Wheezing with LAIV administration occurs primarily in children less than 12 months of age with their first dose.
 - d. Among children 6 to 11 months of age, hospitalization rates for any cause during the 180 days after vaccination were higher with LAIV than with TIV.
2. Regarding the results of the adult study, which of the following statements is false?
 - a. During an influenza season where most circulating viruses were antigenically drifted, TIV was found to be more efficacious than LAIV in preventing laboratory-confirmed symptomatic illnesses from influenza in healthy adults.
 - b. Absolute efficacy against culture-confirmed influenza A was greater for TIV than for LAIV.
 - c. Absolute efficacy against culture-confirmed influenza B was greater for TIV than for LAIV.
 - d. TIV recipients were more likely to report arm soreness and LAIV recipients were more likely to report runny nose/congestion.

1. LAIV was significantly more protective than TIV against both well-matched and mismatched influenza A viruses.
 2. Absolute vaccine efficacy against culture-confirmed influenza A was 74% for either TIV or LAIV.

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