Clinical Insights® in
PEDIATRIC RESPIRATORY CARE
VOLUME 4, NUMBER 11, 2008

PEDRO A. PIEDRA, MD, EDITOR-IN-CHIEF; STAN L. BLOCK, MD, REVIEWER; JENNIFER NISITA, SENIOR EDITOR; MARK PALANGIO, SENIOR MEDICAL WRITER

# Maternal Influenza Immunization Reduces Influenza Illness in Mothers and Their Infants

Influenza infection can result in serious outcomes among both pregnant women and young infants. Maternal influenza infection had been associated with fetal malformations. Influenza infection among infants can lead to hospitalization and secondary complications such as bacterial pneumonia and otitis media. Studies have revealed that natural maternal antibodies protect infants during the first few months of life. Immunization of pregnant women with inactivated trivalent vaccine is recommended by both the Advisory Committee on Immunization Practices and the World Health Organization (WHO). However, influenza vaccines are not approved for use in infants aged <6 months, and antiviral influenza drugs are not approved for children aged <1 year. Therefore, maternal vaccination represents a potential strategy for protecting neonates against influenza infection.

*Studies have revealed that natural maternal antibodies protect infants during the first few months of life.*

Zaman and colleagues conducted a prospective randomized trial evaluating the clinical effectiveness of influenza vaccine administration during pregnancy in Bangladesh, a tropical setting of perennial influenza virus transmission. A total of 340 mothers were randomly assigned to receive an inactivated influenza vaccine (influenza-vaccine group) containing strains for 2004 (A/New Caledonia/20/99 [H1N1], A/Fujian/411/2002 [H3N2] and B/Hong Kong/330/2001), as recommended by the WHO for the southern hemisphere, or the 23-valent pneumococcal polysaccharide vaccine (control group). The primary outcome in infants was the first episode of laboratory-confirmed influenza before 24 weeks of age. Mothers and infants were observed from August 2004 through December 2005.

Influenza immunization in mothers provided statistically significant reductions in the incidence of laboratory-confirmed influenza among their infants. There were significantly fewer cases of laboratory-confirmed influenza among infants of mothers who received influenza vaccine (6 cases in 159 infants) than among infants of mothers in the control group (16 cases in 157 infants), representing a vaccine effectiveness of 63% (95% confidence interval [CI], 5–85; $P<0.05$). There were also significantly fewer cases of respiratory illness with fever in infants born to mothers in the influenza-vaccine group than in the control group (110 vs 153 cases, respectively), representing a vaccine effectiveness of 29% (95% CI, 7–46; $P<0.05$).

*Continued*

**Release Date:** Dec. 4, 2008
**CME Credit Valid Through:** Feb. 4, 2009

This educational activity is conducted as a part of the *Pediatric Respiratory Care Initiative*™ (PRCI™), sponsored by Professional Postgraduate Services® (PPS).

Participants who wish to receive CME credit for this educational activity should do the following: (1) read the current issue; and (2) complete the post-test and evaluation form included to conclude this CME activity. You may also complete the post-test and evaluation form on our website, www.PediatricRespiratory.org, by logging on and selecting "Clinical Insights." You may also return the completed post-test and evaluation via fax to 1 (201) 430-1441 or mail to: **Professional Postgraduate Services®, CME Dept. T328, 200 Meadowlands Parkway, Secaucus, NJ 07094-2302.** If you have any questions, please call 1 (800) 606-6106 Ext. 6019. Applicants will receive a certificate of participation from PPS by return mail within 6 to 8 weeks of the date of receipt of the completed evaluation form and post-test. Online applicants will automatically receive their CME credit certificate upon completion of the post-test and evaluation form.

**LEARNING OBJECTIVES** After studying the literature presented in this issue, participants will be able to:

- Describe the effectiveness of maternal influenza immunization in reducing influenza illness in mothers and their infants
- Describe the risk for developing asthma associated with LAIV in children aged 1.5 to 18 years with or without a history of mild intermittent asthma, reactive airways disease, or wheezing[a]

**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.

Professional Postgraduate Services® is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Professional Postgraduate Services® designates this educational activity for a maximum of 0.50 *AMA PRA Category 1 Credit*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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

**OFF-LABEL DISCLOSURE** Some of the drug treatments discussed in this issue may note uses not approved by the Food and Drug Administration. Articles containing such uses will be noted at the end of the article.

[a]The study by Galani et al (pg 2) was conducted before LAIV was approved for use in the United States. LAIV is currently approved for individuals aged 2 to 49 years. The package insert contains a warning and precaution for LAIV use in children with asthma or recurrent wheezing.

Disclosures:

Dr Piedra is professor of pediatrics and molecular virology and microbiology at Baylor College of Medicine, Houston, Texas. He has indicated that he receives grant/research support from Juvaris BioTherapeutics, Inc., MedImmune, Inc., Sanofi Pasteur, and Novartis Pharmaceuticals; is a speaker for MedImmune, Inc.; and is an ad hoc consultant for MedImmune, Inc., Sanofi Pasteur, Novartis Pharmaceuticals, Hoffmann-La Roche Inc., and Merck & Co., Inc.

Dr Block has indicated that he receives grant/research support from GlaxoSmithKline, MedImmune, Inc., Merck & Co., Inc., Novartis Pharmaceuticals, Inc., and sanofi-aventis; he is a retained consultant and is a member of the speaker bureau for MedImmune, Inc., Merck & Co., Inc., and sanofi-aventis.

PPS Staff: Mark Palangio, senior medical writer; Terri Setteducato, senior program director; and Elizabeth Ward, CME director, have indicated no relevant financial relationships. Jennifer Nisita, senior editor, has indicated that her spouse is a salaried employee of Merck & Co., Inc.

**Maternal Influenza Immunization Reduces Influenza Illness in Mothers and Their Infants** *(Continued)*

Additionally, influenza immunization was associated with a 42% reduction ($P<0.05$) in the rate of infant clinic visits for respiratory illness with fever and a 49% reduction ($P<0.05$) in the rate of clinician testing for influenza. Among the mothers, there was a significant reduction in the rate of respiratory illness with fever of 36% (95% CI, 4–57; $P<0.05$) in the influenza-vaccine group compared with the control group.

This study showed that the inactivated influenza vaccine significantly reduced the incidence of influenza illness in infants younger than 6 months in the tropical setting, while reducing the rate of respiratory illness with fever in mothers. This shows that a single dose of influenza vaccine administered during pregnancy can provide a significant two-for-one benefit to both mothers and their infants.

Zaman K, Roy E, Arifeen SE, et al. Effectiveness of maternal influenza immunization in mothers and infants. *N Engl J Med.* 2008;359(15):1555-1564.



## COMMENTARY

**STAN L. BLOCK, MD, Professor of Clinical Pediatrics, University of Kentucky College of Medicine, Lexington, KY, University of Louisville Medical School, Louisville, KY, President, Kentucky Pediatric/Adult Research, Inc., Bardstown, KY**

*For more than 26 years, I have cajoled and badgered pregnant mothers, incidentally seen in my rural pediatrics office, to receive an influenza vaccine for the protection of both themselves and their newborns. Expert opinion had suggested that the injectable flu vaccine could provide a proverbial "double bang for the buck." I could prevent future flu sick visits from mothers, many of whom were teenagers and still under my care, and also from their babies, who, until reaching 7 months, had no other means of protection. Nothing brings more dread to the busy pediatric practice than the highly febrile newborn younger than 2 months, who in the winter is especially likely to have influenza, untreatable in this age group. Normal office flow grinds to a halt so that all staff can perform a septic workup and transfer the infant to the hospital. Lots of sweat and more gray hairs for me!*

*The Zaman paper provides conclusive formal evidence that our perceptions on this issue were accurate—influenza vaccine for pregnant women is a veritable two-for-one immunization. (It's nice to be right once in awhile!) The study showed that with vaccination in pregnancy, passive flu protection occurs in nearly two-thirds of infants, with 5-6 month durability. Although the maternal influenza vaccine continues to be a tough sell (<15% nationwide), these findings strengthen our conviction. Now, if only I could persuade mothers who have not received routine Tdap and HPV4 vaccines to be inoculated postpartum! In a way, these vaccines also have a two-for-one benefit, offering vital prevention in the mother and simultaneous protection to the infant. Tdap ensures that the neonate is protected from exposure to maternal whooping cough (a transmission route accounting for more than 25% of cases); and HPV4 may reduce cases of perinatally contracted respiratory papillomatosis by 90%.*



# Intranasal, Trivalent, Live Attenuated Influenza Vaccine Did Not Increase the Risk for Asthma in Children

The intranasal, trivalent, live attenuated influenza vaccine (LAIV) is approved for use in children aged ≥2 years without high-risk conditions for influenza-related complications. However, the safety of the LAIV in children with asthma is unclear.

In a 4-year, open-label, field trial conducted from 1998–1999 to 2001–2002, Gaglani et al assessed the safety of the then investigational LAIV in recipients aged 1.5 to 18 years who were members of a healthcare organization in central Texas. The cohort was divided into two groups: those with a history of intermittent wheezing (including mild intermittent asthma, reactive airways disease, or wheezing) and those without such a history. During a 4-year trial, children with a history of intermittent wheezing received single annual LAIV doses. Children

*Continued*

## Intranasal, Trivalent, Live Attenuated Influenza Vaccine Did Not Increase the Risk for Asthma in Children *(Continued)*

with intermittent wheezing were defined as those with a history of asthma, reactive airway disease or wheezing who did not use steroids (oral or inhaled) or bronchodilator therapy daily or every other day for asthma control, and were not hospitalized or seen in the emergency room in the past 12 months (past 6 months if aged <2 years).

During each of the 4 years, 454, 656, 656, and 430 children, respectively, with intermittent wheezing who received LAIV had no increased risk for medically attended acute respiratory illnesses, including acute asthma exacerbation in the first 2 and 6 weeks post-LAIV for children belonging to three specified age groups (1.5–4 years; 5–9 yrs; and 10–18 yrs) and for children of all ages together. There was also no increased risk of acute respiratory illnesses among first-dose LAIV recipients, including those aged 1.5 to 4 years, and those receiving two to four consecutive annual doses. Further, children with parents' report of intermittent wheezing and those with administrative ICD-9 codes for asthma during the 2 years prior to receiving LAIV had no increased risk for asthma exacerbations.

During each of the 4 years, 2,952, 3,092, 2,953, and 2,478 children, respectively, without a history of wheezing received LAIV and had no increased risk of new-onset asthma.

The findings of this open-label trial suggested that LAIV administration was safe and well tolerated in children aged 1.5 to 18 years with or without a history of mild intermittent asthma, reactive airways disease, or wheezing. Children with such a history did not experience an increased risk for medically attended acute respiratory illnesses or acute asthma exacerbations with either the first LAIV dose or four subsequent annual doses. Similarly, children without a history of wheezing did not experience new-onset asthma, with the first dose or subsequent annual dose.

Gaglani MJ, Piedra PA, Riggs M, Herschler G, Fewlass C, Glezen WP. Safety of the intranasal, trivalent, live attenuated influenza vaccine (LAIV) in children with intermittent wheezing in an open-label field trial. *Pediatr Infect Dis J.* 2008;27(5):444-452.

## *Clinical Insights® in Pediatric Respiratory Care* Post-Test

1. In the controlled study conducted by Zaman et al, maternal influenza immunization resulted in which of the following?
   a. A significant reduction in the rate of respiratory illness with fever among infants but not among mothers
   b. A significant reduction in the rate of respiratory illness with fever among mothers but not among infants
   c. A significant reduction in the rate of respiratory illness with fever among both infants and mothers
   d. No reduction in the rate of respiratory illness with fever among infants or mothers

2. In the open-label study conducted by Gaglani et al, children aged 1.5 to 18 years with a history of intermittent wheezing who were given intranasal LAIV experienced which of the following?
   a. An increased risk for medically attended acute respiratory illnesses
   b. An increased risk for acute asthma exacerbations
   c. An increased risk for both medically attended acute respiratory illnesses and acute asthma exacerbations
   d. No increased risk for medically attended acute respiratory illnesses or acute asthma exacerbations

### ANSWERS

**Question 1 answer: c.** Among infants, there was a significant 29% reduction in cases of respiratory illness with fever with maternal influenza immunization. Similarly, among mothers, there was a significant 36% reduction in cases of respiratory illness with fever with maternal influenza immunization.

**Question 2 answer: d.** Children with a history of intermittent wheezing did *not* experience an increased risk for medically attended acute respiratory illnesses or acute asthma exacerbations resulting from LAIV.

In addition to regular issues of *Clinical Insights® in Pediatric Respiratory Care*, visit **www.PediatricRespiratory.org** for information about upcoming CME activities.



### 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.

**Activity Code:** T328-11 **Issue Date:** Dec. 4, 2008 **Valid Through:** Feb. 4, 2009

# CME Activity Evaluation/Registration Form

Participants who wish to obtain CME credit, please complete the contact information below, sign this form, and fax it with the completed post-test to 1 (201) 430-1441 or mail to PPS, CME Dept. T328, 200 Meadowlands Parkway, Secaucus, NJ 07094-2302. You may download previous issues of *Clinical Insights® in Pediatric Respiratory Care* e-newsletters by visiting us online at **www.PediatricRespiratory.org.**

I have participated in this activity as designed and am claiming _____ *AMA PRA Category 1 Credit*™ (maximum 0.50)

_____

*(Signature)* *(Date)*

**PLEASE PRINT CLEARLY**

☐ Dr ☐ Mr ☐ Mrs ☐ Ms ☐ Prof Other *(Please specify)* _____

First Name

Last Name

Degree ☐ MD ☐ PharmD ☐ DO ☐ NP ☐ PA ☐ RPh ☐ Other *(Please specify)* _____

Specialty ☐ Family Practice ☐ Pediatrics ☐ General Practice ☐ Neonatal ☐ Other *(Please specify)* _____

Profession

**PREFERRED MAILING ADDRESS** ☐ Home ☐ Office ☐ Practice ☐ Academic

Dept/Div/Suite/Unit/Affil

Street

City/State/ZIP Code Country

Email

*(Please print clearly)*

Phone: ___-___-____ Fax: ___-___-____

## Overall Program

| | Strongly Disagree | | Disagree | Agree | | Strongly Agree |
|---|---|---|---|---|---|---|
| 1. This activity met the stated objectives in such a way that I am better able to: | | | | | | |
| a. Describe the effectiveness of maternal influenza immunization in reducing influenza illness in mothers and their infants | 1 | 2 | 3 | 4 | 5 | 6 |
| b. Describe the risk for developing asthma associated with LAIV in children aged 1.5 to 18 years with or without a history of mild intermittent asthma, reactive airways disease, or wheezing | 1 | 2 | 3 | 4 | 5 | 6 |
| 2. Please rate the following statements: | | | | | | |
| a. Potential benefits to newborns from maternal vaccinations during pregnancy and postpartum | 1 | 2 | 3 | 4 | 5 | 6 |
| b. Vaccine-virus induced wheezing | 1 | 2 | 3 | 4 | 5 | 6 |

3. Did the activity present a balanced view of therapeutic options available for the disease state(s)? ☐ Yes ☐ No*
   * If you checked "No," please explain. _____

4. Did the activity present content that fairly represented and was based on a reasonable and valid interpretation of the information available on the subject? ☐ Yes ☐ No*
   * If you checked "No," please explain. _____

5. Did the activity appear to place an unreasonable emphasis on one particular product/service? ☐ Yes* ☐ No
   * If you checked "Yes," please explain. _____

6. In reflecting on your practice, what type of impact will this educational activity have? *(Select all that apply.)* I will:
   - ☐ Be aware of the ability of maternal influenza immunization to reduce influenza illness in mothers and their infants.
   - ☐ Recognize that LAIV administration is safe and well tolerated in children aged 1.5 to 18 years with or without a history of mild intermittent asthma, reactive airways disease, or wheezing. (The study by Gaglani et al was conducted before LAIV was approved for use in the United States. LAIV is currently approved for individuals aged 2 to 49 years. The package insert contains a warning and precaution for LAIV use in children with asthma or recurrent wheezing.)
   - ☐ Other *(please specify)* _____

7. What topics should be dealt with in more detail? *(Select all that apply.)*
   - ☐ Seasonal influenza immunization guidelines
   - ☐ Reactive airway disease in children
   - ☐ Other (please specify) _____

8. What is the most important thing you learned from this activity?_____

Thank you for your participation.