

## Clinical pearls for preventing, diagnosing, and treating seasonal and 2009 H1N1 influenza infection in patients with asthma

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Concern about infection with influenza has heightened after the initial and ongoing circulation of a 2009 H1N1 influenza strain. The goal of this article is to discuss clinical pearls that will assist clinicians in preventing, diagnosing, and managing influenza infections.

### SHOULD PATIENTS WITH ASTHMA BE VACCINATED FOR SEASONAL INFLUENZA? WHAT DO WE NEED TO KNOW ABOUT THE 2009 H1N1 INFLUENZA?

Asthma is currently listed as a high-risk condition for influenza infection by the Centers for Disease Control and Prevention; those with asthma are recommended to receive the seasonal influenza vaccination.<sup>1</sup> Authors of a recent review of the topic determined that uncertainty remains regarding the protection that influenza vaccine provides against asthma exacerbations.<sup>2</sup> This conclusion relies heavily on a randomized, double-blind placebo controlled trial that found seasonal influenza vaccination did not decrease asthma exacerbations compared with placebo vaccination.<sup>3</sup> Influenza vaccination can be expected to reduce the role of influenza infections in patients with asthma.

A 2009 H1N1 influenza strain began circulating in April 2009 and became widespread in June 2009. Immunologic protection against seasonal influenza strains does not protect against 2009 H1N1 influenza. Therefore, separate vaccine development for 2009 H1N1 has occurred, and clinical trials are ongoing. A significant number of hospitalizations for 2009 H1N1 have occurred in patients with asthma and other chronic respiratory diseases. These groups are targeted for 2009 H1N1 vaccination according to the Centers for Disease Control and Prevention:

- **Pregnant women** because they are at higher risk of complications and can potentially provide protection to infants who cannot be vaccinated.
- **Household contacts and caregivers for children younger than 6 months of age** because younger infants are at higher

#### Abbreviations used

LAIV: Live attenuated influenza vaccine  
TIV: Trivalent inactivated vaccine

risk of influenza-related complications and cannot be vaccinated. Vaccination of those in close contact with infants younger than 6 months old might help protect infants by cocooning them from the virus.

- **Health care and emergency medical services personnel** because infections among health care workers have been reported, and this can be a potential source of infection for vulnerable patients. Also, increased absenteeism in this population could reduce health care system capacity.
- **All people from 6 months through 24 years of age:**
  - **Children from 6 months through 18 years of age** because cases of 2009 H1N1 influenza have been seen in children who are in close contact with each other in school and day care settings, which increases the likelihood of disease spread.
  - **Young adults 19 through 24 years of age** because many cases of 2009 H1N1 influenza have been seen in these healthy young adults; they often live, work, and study in close proximity; and they are a frequently mobile population.
- **Persons age 25 through 64 years who have health conditions associated with a higher risk of medical complications from influenza.**

The Centers for Disease Control and Prevention has set up a web site for information pertaining to 2009 H1N1 (<http://www.cdc.gov/H1N1>), and the American Academy of Allergy, Asthma & Immunology displays frequent updates regarding influenza topics (<http://www.aaaai.org>).

### HOW SHOULD PATIENTS WITH ASTHMA BE VACCINATED FOR SEASONAL OR 2009 H1N1 INFLUENZA?

Patients with asthma should receive the trivalent inactivated vaccine (TIV) intramuscularly. Adults and children >3 years old should receive 0.5 mL per dose, and those <3 years old should receive 0.25 mL. Adults and older children should be injected in the deltoid, infants and younger children in the anterior-lateral thigh. Patients <9 years old with no previous seasonal influenza vaccine should receive a booster vaccine 4 weeks after the initial dose.

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Live attenuated influenza vaccine (LAIV) is administered as an intranasal spray and is recommended for healthy patients who are 2 to 49 years old. LAIV is not currently recommended for patients with asthma primarily because of concerns about triggering an asthma exacerbation. If there is a TIV shortage or a very strong preference for nasal over intramuscular delivery, we recommend a discussion of the potential risks and benefits and consideration of LAIV in patients with asthma.

Details about the 2009 H1N1 influenza vaccine are preliminary. Both TIV and LAIV will be available; preliminary data suggest that only children <9 years old will need a booster vaccination 3 weeks after the initial 2009 H1N1 vaccination. Additional information will be made public via the Centers for Disease Control and Prevention web site (<http://www.cdc.gov/H1N1>).

### **WHAT IF A PATIENT WITH ASTHMA IS ALLERGIC TO EGG OR HAS A HISTORY OF AN ALLERGIC REACTION TO INFLUENZA VACCINATION?**

Contraindication and precautions for influenza vaccination include a current moderate to severe febrile illness, a history of Guillain-Barré syndrome within 6 weeks of a previous influenza vaccination, a history of severe allergy to chicken egg, and a history of severe reaction to the influenza vaccination. For those with egg allergy or a history of a hypersensitivity reaction to previous influenza vaccine, we recommend an evaluation by an allergist/immunologist.

If a patient reports an allergy to egg, it is important to attempt to distinguish an egg intolerance (which is not a contraindication to vaccination) from a true hypersensitivity reaction. Seasonal and 2009 H1N1 influenza vaccines may contain egg protein, although the concentration of egg protein may not be known and may vary by year, manufacturer, and lot. A previous study suggests that patients with egg allergy (as defined by a convincing clinical history plus either positive skin testing or positive oral challenge testing to egg) can safely receive an influenza vaccine when egg protein is <1.2 µg/mL, a skin prick test to neat influenza vaccine is negative, and the vaccine is administered in split dosing (1/10 dose and 9/10 dose).<sup>4</sup> If the egg protein concentration for seasonal and 2009 H1N1 influenza vaccine is unknown, we recommend a skin prick test to egg when the diagnosis of egg allergy is in question. If skin prick testing to egg is negative, one may consider checking serum-specific IgE levels to egg in select patients with compelling histories. If egg allergy is excluded and there is no previous reaction to influenza vaccination, we recommend proceeding to full-dose vaccination with a 30-minute observation period in a setting in which anaphylaxis can be promptly evaluated and treated.

For those with confirmed or strongly suspected egg allergy, we recommend influenza vaccine testing with a neat prick skin test and a 1:100 dilution intradermal test. There may be an irritant response rate of about 15% to a 1:100 intradermal influenza vaccine skin test. If skin tests are negative, we recommend proceeding to full-dose vaccination with a 30-minute observation period in a setting in which anaphylaxis can be promptly evaluated and treated. If skin tests to influenza vaccine are positive, we recommend a discussion of risks and benefits with the patient. If, after this discussion, it is determined that the benefits outweigh the risks, we recommend proceeding with the following intramuscular graded dose challenge protocol:

1. 0.05 mL 1:10 vaccine
2. 0.05 mL neat vaccine
3. 0.1 mL neat vaccine
4. 0.15 mL neat vaccine
5. 0.2 mL neat vaccine

A graded dose challenge protocol should only be conducted in a setting in which anaphylaxis can be promptly evaluated and treated. Data on the risk of allergic-type reactions with subsequent vaccination (either booster vaccination in the same season or subsequent annual vaccination) are limited. We suggest repeat skin testing because lot-to-lot variability in egg protein concentration and other potentially allergic constituents of the vaccine is unknown. Until more information is available about the 2009 H1N1 influenza vaccine, we suggest modeling such an evaluation after seasonal influenza vaccine allergy evaluations.

### **WHAT ARE SIDE EFFECTS OBSERVED WITH THE SEASONAL INFLUENZA VACCINE? ARE PATIENTS WITH ASTHMA AT A HIGHER RISK FOR SIDE EFFECTS AFTER INFLUENZA VACCINATION THAN PATIENTS WITHOUT ASTHMA?**

Anaphylaxis is estimated to occur after 1 in 1,000,000 influenza vaccinations. More common side effects include injection site pain, fever, malaise, myalgias, and headache. Patients with red eyes, mild upper facial swelling, and mild upper respiratory symptoms such as sore throat, cough, and hoarseness (and no other symptoms or signs of an allergic reaction) after previous influenza vaccinations can receive the influenza vaccine without further evaluation.

The TIV does not appear to increase the risk of an asthma exacerbation in the 2 weeks after vaccination.<sup>5</sup> Uncertainty remains regarding the potential side effects of LAIV in young children with asthma given the conflicting results of currently available studies.

### **HOW CAN WE HELP IMPROVE VACCINATION RATES FOR GROUPS LIKE PATIENTS WITH ASTHMA WHO ARE CONSIDERED AT HIGH RISK FOR INFLUENZA COMPLICATIONS?**

Vaccination rates for patients with asthma range from 29% to 48%. If available, clinicians should consider using reminder systems, standing orders, or other systems that identify and contact patients with asthma. Another strategy may include increased awareness of influenza vaccination in a coordinated effort with National Influenza Vaccination Week (December 6-12, 2009).

### **WHAT SYMPTOMS SUGGEST INFLUENZA INFECTION IN PATIENTS WITH ASTHMA?**

Patients with asthma infected with influenza may experience symptoms of fever, cough, sore throat, nasal congestion, rhinorrhea, myalgias, headache, chills, fatigue, vomiting, and diarrhea. Signs or symptoms of a lower respiratory infection such as dyspnea are concerning and should prompt urgent evaluation. Other types of viral infections commonly trigger asthma exacerbations and may mimic influenza infections. Awareness of local circulating influenza infection rates can be helpful in predicting the likelihood of influenza infection in patients with asthma.

## WHICH PATIENTS WITH ASTHMA SHOULD BE TESTED FOR SEASONAL AND H1N1 INFLUENZA?

Patients with asthma and influenza-like illness should be tested when diagnosis is in question, or when the result will influence a decision about antiviral medication, antibacterial medication, or infection control. Advantages of testing may include improved accuracy of diagnosis (limits potentially unnecessary antiviral medication prescription), guidance of antiviral choice, and improved community surveillance data. Advantages of not testing include keeping patients away from medical settings (potentially decreasing virus spread) and cost savings.

## WHICH TESTS ARE RECOMMENDED TO DETECT SEASONAL AND H1N1 INFLUENZA?

RT-PCR testing is recommended because it provides fast turnaround (4-6 hours) and strain information.<sup>4</sup> We recommend RT-PCR testing if available for patients with asthma because strain information may be important when faced with limited antiviral choices. Rapid influenza diagnostic tests give results in 30 minutes but have a low sensitivity to detect virus, particularly 2009 H1N1 influenza (sensitivity may be as low as 10%). Therefore, a negative rapid test should not be used to rule out 2009 H1N1 influenza. For older children and adults, nasopharyngeal swabs are the preferred collection method. In infants and young children, nasal aspiration and swabs are the preferred collection methods. Oropharyngeal swabs may have lower sensitivity than the preferred collection methods, but they remain an acceptable method of collection.

## HOW SHOULD INFLUENZA IN PATIENTS WITH ASTHMA BE TREATED?

Patients with asthma who have suspected or confirmed influenza should be strongly considered for antiviral medications because of their increased risk of developing a complication of influenza. Data from randomized controlled trials for antiviral medications for patients with asthma are limited; 1 trial demonstrated a decreased risk of asthma exacerbation (defined by changes in peak flow) in the oseltamivir group compared with placebo but did not meet its primary endpoint of demonstrating a difference in time to freedom from illness.<sup>7</sup>

Patients with asthma who present with concerning signs and symptoms of lower respiratory tract infection and suspected influenza should be treated with antiviral medication even if more than 48 hours have elapsed since symptoms started. In addition, patients with asthma should be treated for asthma exacerbation per their personalized written asthma action plan. Complications of influenza infection such as bacterial pneumonia should be considered. Evaluation of fatal pediatric 2009 H1N1 influenza cases found *Staphylococcus aureus* to be the most common bacteria isolated (including some cases of methicillin-resistant *S aureus*).

Antiviral medication choice depends on the influenza strain type and resistance patterns. Strain type can be obtained directly from test results (if the RT-PCR technique is used) or can be estimated by community surveillance reports. Seasonal influenza A H1N1-type (not 2009 H1N1) is resistant to oseltamivir, whereas type A H3N2-type is not. The influenza type B strain that circulated in the 2008 to 2009 season was susceptible to oseltamivir. Two of the type A strains that circulated most in the

2008 to 2009 season are expected to circulate in the 2009 to 2010 season and are included in the 2009 to 2010 seasonal influenza vaccine. Current recommendations are based on 2008 to 2009 season circulation and resistance data and will be updated when additional data become available.

Oseltamivir is recommended for influenza B, influenza A H3N2-like, and 2009 H1N1. Zanamivir or a combination of rimantadine and oseltamivir is recommended for influenza A seasonal H1N1-like because of oseltamivir resistance. If the chosen testing method does not distinguish between influenza A strains, a combination of oseltamivir and rimantadine is recommended for patients with asthma. If novel H1N1 influenza is the dominant circulating strain and antiviral resistance does not emerge, oseltamivir may become the recommended antiviral for strains that cannot be confirmed. Zanamivir is active against all currently circulating influenza strains but should be used cautiously in patients with asthma because of case reports of severe bronchospasm. Oseltamivir is the preferred antiviral medication for pregnant patients and children <7 years old. Rimantadine may be considered for patients with asthma who are pregnant or <7 years old after weighing the risks of potential side effects with the potential benefits of more effective antiviral clearance.

Patients with asthma who are not vaccinated against influenza at the time of diagnosis should be offered vaccination with TIV (for seasonal or 2009 H1N1) along with antiviral treatment. Those with fever should not be vaccinated until the fever resolves.

## WHEN SHOULD PATIENTS WITH ASTHMA RECEIVE ANTIVIRAL CHEMOPROPHYLAXIS FOR INFLUENZA?

Patients with asthma who are in close contact with known influenza cases should be offered vaccination with TIV and continue chemoprophylaxis for 10 days beyond the time of exposure. If the patient is <9 years old and has not received influenza vaccine in previous seasons (requires a booster vaccination), chemoprophylaxis should be continued for 2 weeks after the booster vaccination.

### Conclusions and key points for patients with asthma:

1. Vaccinate with seasonal and 2009 H1N1 TIV unless there is a strong contraindication such as current febrile illness or Guillain-Barré syndrome within 6 weeks of previous influenza vaccination.
2. Patients with asthma concerned about influenza vaccine allergy (including a convincing clinical history of egg allergy) should be evaluated by an allergist/immunologist.
3. Consider whether testing for influenza will change treatment recommendations; when testing, strongly consider the RT-PCR testing method.
4. Treat asthma patients with antiviral medications based on circulating strains and resistance patterns.

### REFERENCES

1. Prevention and control of seasonal influenza with vaccines. MMWR Recomm Rep 2009;58:1-52.

2. Cates CJ, Jefferson T, Rowe BH. Vaccines for preventing influenza in people with asthma. *Cochrane Database Syst Rev* 2009;3:1-49.
3. Bueving HJ, Bernsen RMD, de Jongste JC, van Suijlekom-Smit LW, Rimmelzwaan GF, Osterhaus ADME, et al. Influenza vaccination in children with asthma: randomized double-blind placebo-controlled trial. *Am J Respir Crit Care Med* 2004; 169:488-93.
4. James JM, Zeiger RS, Lester MR, Fasano MB, Gern JE, Mansfield LE, et al. Safe administration of influenza vaccination to patients with egg allergy. *J Pediatr* 1998;133:624-8.
5. The safety of inactivated influenza vaccine in adults and children with asthma. *N Engl J Med* 2001;345:1529-36.
6. Harper SA, Bradley JS, Englund JA, File TM, Gravenstein S, Hayden FG, et al. Seasonal influenza in adults and children—diagnosis, treatment, chemoprophylaxis and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis* 2009;48:1003-32.
7. Johnston SL, Ferrero F, Luz Garcia M, Dutkowski R. Oral oseltamivir improves pulmonary function and reduces exacerbation frequency for influenza-infected children with asthma. *Pediatr Infect Dis J* 2005;24:225-32.