

Seasonal Influenza Prevention and Treatment

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Learning Objectives

1. Identify groups and high-risk individuals for whom the Advisory Committee on Immunization Practices recommends annual influenza immunization.
2. List the differences between trivalent inactivated influenza and live attenuated influenza vaccines, appropriate recipients of these vaccines, and the contraindications to each.
3. Recognize public health and clinical tools to assist in the identification of influenza in patients.
4. Describe how and when to use antiviral medications for influenza.
5. Develop and apply effective approaches to encourage healthcare professionals to be vaccinated annually against influenza.

Introduction

Influenza is a leading cause of morbidity and mortality in the United States and results in significant economic costs and loss of productivity.¹ The World Health Organization (WHO) estimates there are approximately 25 to 50 million US cases per year, resulting in 150,000 hospitalizations and as many as 30,000 to 40,000 deaths.² A study of the economic effect of influenza cases in 2003 found that annual influenza epidemics result in an average of 610,330 life-years lost, 3.1 million hospitalized days, 31.4 million outpatient visits, direct medical costs averaging \$10.4 billion, and projected lost earnings of \$16.3 billion.³

Most individuals will recover from influenza infection within 1 to 2 weeks of symptom onset without seeking medical treatment, but some are at greater risk of complications. Rates of serious illness and death are highest among individuals younger than 2 years, 65 years or older, and with medical conditions that increase the risk of complications. Influenza virus infection can lead to primary viral pneumonia, co-infection with other viral or bacterial pathogens, exacerbation of co-existing medical conditions, or secondary bacterial pneumonia.⁴

The timing, duration, and intensity of seasonal influenza vary each year, but localized outbreaks can occur as early as October. The US influenza season and corresponding epidemics typically begin in late fall and continue through early spring, with peak activity typically occurring in January or February.⁴ The American Academy of Family Physicians, the American Academy of Pediatrics, the American College of Obstetricians and Gynecologists, the Advisory Committee on Immunization Practices (ACIP), the Centers for Disease Control and Prevention (CDC), the WHO, and many other organizations recommend that all individuals between the ages of 6 months and 18 years, as well as those over 50 years, and all those with medical conditions that place them at increased risk of complications, be vaccinated against influenza infection each year; yet vaccination rates remain low.

Annual Influenza Immunization Recommendations

Vaccination is associated with a 60% reduction in influenza-related morbidity and a 70% to 80% reduction in mortality.² Eighty-three percent of the US population is currently included in one or more of the groups for which the ACIP recommends annual influenza immunization. Target groups include anyone at risk of medical complications resulting from influenza or individuals more likely to need medical care, as well as all individuals who live with or care for individuals at high risk of complications. Although vaccination is recommended for anyone desiring to avoid influenza-associated illness, individuals in the target groups in particular should be vaccinated annually.⁴ *Table 1* provides a list of individuals and high-risk groups for whom annual vaccination is recommended; children and individuals 65 years and older are discussed below.

Children

With the exception of individuals older than 65 years, those younger than 2 years experience higher rates of influenza-related morbidity than any other age group. Hospitalization rates resulting from severe illness have been as high as 3 per 1,000 in individuals between the ages of 6 and 23 months, and 9 per 1,000 in individuals younger than 6 months.⁵ Because influenza vaccines are not approved by the Food and Drug Administration (FDA) for use in children 6 months and younger, priority should be placed on vaccinating individuals who come in close contact with these children⁴; strategies to accomplish this include vaccinating pregnant women, fathers, and all household members.⁶ Beginning with the 2008-09 influenza season, the ACIP recommends annual influenza vaccination for all individuals between the ages of 6 months and 18 years.⁴

Individuals 65 Years and Older

Rates of hospitalization during the influenza season are significantly higher in individuals over the age of 65 years⁴, and most influenza-associated mortalities occur among those over the age of 65 years.² Between 1976 and 2001, an estimated 32,651 influenza-related deaths occurred annually among adults older than 65 years.⁴

Residents of nursing homes and other long-term care facilities are at increased risk of influenza-related complications.⁴ The ACIP recommends vaccination of all volunteers and staff of nursing homes and long-term care facilities beginning in October of each year and continuing through the influenza season as long as vaccine supplies are available.⁷

Trivalent Inactivated and Live Attenuated Influenza Vaccines

Each year, the WHO's Global Influenza Surveillance Network analyzes data collected on circulating influenza viruses and provides



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Table 1. Groups Who Should Receive Annual Vaccination

- **Individuals ages 6 months to 18 years**
- **Individuals at risk of medical complications**
 - All individuals > 50 years
 - Individuals ages 6 months to 18 years who are receiving long-term aspirin therapy and who might be at risk for experiencing Reye's syndrome after influenza virus infection
 - Women who will be pregnant and/or breastfeeding during the influenza season
 - Adults and children who have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, hematological, or metabolic disorders (including diabetes)
 - Adults and children who have suppressed immune systems (including those caused by medications or by human immunodeficiency virus infection)
 - Adults and children who have any condition (eg, cognitive dysfunction, spinal cord injuries, seizure disorders, or other neuromuscular disorders) that can compromise respiratory function or the handling of respiratory secretions or that can increase the risk for aspiration
 - Residents of nursing homes and other chronic-care facilities
- **Individuals who live with or care for individuals at high risk for influenza-related complications**
 - Healthcare professionals
 - Healthy household contacts (including children) and caregivers of children age < 59 months (ie, age < 5 years) and adults age > 50 years; and
 - Healthy household contacts (including children) and caregivers of persons with medical conditions that confer higher risk for severe complications from influenza.

From: Fiore AE, Shay DK, Haber P, et al. Prevention and Control of Influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008. *MMWR* 2007;56[No. RR-6].

a new vaccine formula that will effectively target the three influenza strains most likely to be in wide circulation (<http://www.who.int/immunization/topics/influenza/en/index.html>). Two types of vaccines are currently recommended for use in preventing influenza: trivalent inactivated influenza vaccine (TIV) and live attenuated influenza vaccine (LAIV).⁴ The components for TIV and LAIV prepared for the 2008-09 season will include A/Brisbane/59/2007 (H1N1)-like, A/Brisbane/10/2007 (H3N2)-like, and B/Florida/4/2006-like antigens.⁴

Healthy, non-pregnant individuals between the ages of 2 and 49 years can be given either vaccine.⁴ *Table 2* provides a comparison between TIV and LAIV.

Children younger than age 9 years who are being given vaccine for the first time should receive 2 doses at least 4 weeks apart in order to provide adequate protective antibody response.⁴

Trivalent Inactivated Influenza Vaccine

Trivalent inactivated influenza vaccine is administered via intramuscular injection. It contains noninfectious, killed viruses that cannot cause influenza and is approved by the FDA for use in individuals older than age 6 months.⁴ Since LAIV is not approved for use in those younger than 24 months, infants and children between the ages of 6 months and 2 years should only receive TIV. The ACIP recommends that all individuals between the ages of 6 months and 18 years receive an annual influenza vaccine. Several studies support the safety of administering TIV annually to children and adolescents.⁴ In spite of

this recommendation, as of January 31, 2005, only 48% of all children between the ages of 6 and 23 months had been vaccinated.⁴

A large retrospective study of the safety of TIV in 45,356 children ages 6 to 23 months examined the occurrence of medically attended events following vaccination, including acute upper respiratory tract infection, asthma, cough, gastritis, otitis media, and pneumonia. The study found that vaccination was not associated with statistically significant increases in medically attended events.⁵ A 2008 review of reports to the Vaccine Adverse Event Reporting System (VAERS) indicates that the most common events following TIV administration were fever, injection-site reaction, and rash.⁴ A study of reports made to VAERS between 2004 and 2006 indicates that a small risk of febrile seizures also existed following vaccination with TIV.⁸

Trivalent inactivated influenza vaccine is not recommended for use in the following individuals:

- Those with anaphylactic hypersensitivity to eggs or other vaccine components
- Those with moderate to severe acute febrile illness (defer vaccination until symptoms have resolved)
- Those who have had Guillain-Barre Syndrome (GBS) within 6 weeks following a previous dose.

For those in which TIV is contraindicated, consider prophylactic use of antiviral agents.⁴

In the event of a shortage of TIV, the CDC provides guidance for prioritizing administration; the guidelines can be found at http://www.cdc.gov/flu/professionals/vaccination/vax_priority.htm.

Live Attenuated Influenza Vaccine

Live attenuated influenza vaccine contains live but attenuated, cold-adapted influenza viruses that cannot replicate outside the upper respiratory tract. LAIV is approved by the FDA for use only in healthy individuals between the ages of 2 and 49 years.⁴

Live attenuated influenza vaccine is administered via nasal spray rather than through intramuscular injection. Possible advantages to the use of LAIV include ease of administration, especially among younger patients, and the vaccine's potential to induce a broad and systemic immune response in children.⁴

Individuals who should not receive LAIV include:

- Pregnant women
- Individuals with a history of GBS
- Individuals younger than 2 years or older than 49 years;
- Individuals with hypersensitivity (including anaphylaxis) to eggs or LAIV components
- Children taking aspirin or other salicylates (because of the association of Reye's syndrome with wild-type flu virus infection)
- Individuals with underlying medical conditions including anemia; metabolic diseases such as diabetes; renal dysfunction; hemoglobinopathies; and known or suspected immunodeficiency diseases or immunosuppressive states⁴
- Individuals with asthma, active wheezing, or reactive airway disease or other chronic disorders of the pulmonary or cardiovascular systems
- Children younger than 5 years with recurrent wheezing, because of the potential for increased risk of wheezing post-vaccination unless the potential benefit outweighs the potential risk

The presence of minor illnesses such as diarrhea or mild upper respiratory tract infection, with or without fever, is not a contraindication to the use of TIV or LAIV. All children between 6 months and 9 years of age who have never been vaccinated with TIV or LAIV should receive 2 doses of age-appropriate vaccine in the same season, with a single dose during subsequent seasons.⁴ If prohibitive

nasal congestion is present at the time of vaccination, use of TIV may be indicated.

Antiviral Medications

Influenza antiviral medications are not meant to be substitutes for vaccination, but they are valuable as second-line agents in the prevention and treatment of influenza. In adults, antibodies develop approximately 2 weeks after vaccination. If vaccination of high-risk individuals occurs after influenza activity is active in a community, consider administration of antivirals for chemoprophylaxis until immunity has developed. Children younger than 9 years who receive influenza vaccination for the first time may require up to 6 weeks of chemoprophylaxis.⁴ Table 3 provides recommendations for using antiviral medications for treatment and chemoprophylaxis of influenza.

Oseltamivir (Tamiflu) and zanamivir (Relenza) are the only FDA-approved influenza antiviral medications recommended for use in the United States during the 2008-2009 influenza season.

Oseltamivir and zanamivir are neuraminidase inhibitors that have activity against both influenza A and B viruses. Oseltamivir is FDA-approved for treatment and prophylaxis of individuals 1 year of age and older. Zanamivir is FDA-approved for treatment of individuals 7 years of age and older and approved for use as chemoprophylaxis in individuals 5 years of age and older.⁴

In recent years, a high proportion of influenza viruses circulating in the United States have been resistant to the adamantanes (amantadine, rimantadine); therefore, the CDC recommends that neither amantadine nor rimantadine be used for the treatment or chemoprophylaxis of influenza in the United States during the 2008-2009 influenza season.⁴

Because influenza antiviral medications have not been shown to be effective if administered more than 48 hours after symptom onset, treatment should begin as soon as possible after symptoms appear. When started within the first 48 hours after symptom onset, antiviral medications can reduce illness severity and decrease the duration of illness by approximately 1 day; however, the greatest benefit occurs if therapy is started within the first 30 hours of symptom onset.⁴

Limited data suggest that influenza antiviral medications also may prevent serious influenza-related complications such as bacterial or viral pneumonia or exacerbation of chronic diseases. The recommended duration of treatment with oseltamivir or zanamivir is 5 days. To be maximally effective as prophylaxis, an antiviral drug must be taken daily for the duration of influenza activity in the community. Consider use of antiviral prophylaxis in:

- Individuals at high risk of complications from influenza who are vaccinated after influenza activity has begun (antivirals needed for only 2 weeks following vaccination)
- Individuals younger than 9 years, if being vaccinated for the first time, should receive antivirals until 2 weeks following the second dose of vaccine; antiviral use in those younger than 9 years should be limited to those who are at high risk of complications
- Individuals who provide care to high-risk patients and are not immunized

Table 2. Live Attenuated Influenza Vaccine (LAIV) Compared With Trivalent Inactivated Influenza Vaccine (TIV) for Seasonal Influenza, United States Formulations

Factor	LAIV	TIV
Route of administration	Intranasal spray	Intramuscular injection
Type of vaccine	Live-attenuated virus	Killed virus
Frequency of administration	Annually ^a	Annually ^a
Approved age	Individuals ages 2–49 yrs ^b	Individuals ages >6 months
Interval between 2 doses recommended for children ages >6 months–8 years who are receiving influenza vaccine for the first time	4 weeks	4 weeks
Can be administered to individuals with medical risk factors for influenza-related complications ^b	No	Yes
Can be administered to children with asthma or children ages 2–4 years with wheezing during the preceding year ^c	No	Yes
Can be administered to family members or close contacts of immunosuppressed persons not requiring a protected environment	Yes	Yes
Can be administered to family members or close contacts of immunosuppressed persons requiring a protected environment (e.g., hematopoietic stem cell transplant recipient)	No	Yes
Can be administered to pregnant women	No	Yes
Can be simultaneously administered with other vaccines	Yes ^d	Yes ^e

^a Children ages 6 months to 8 years who have never received influenza vaccine before should receive 2 doses. Those who only receive 1 dose in their first year of vaccination should receive 2 doses in the following year, spaced 4 weeks apart.

^b Persons at high risk for complications of influenza infection because of underlying medical conditions should not receive LAIV.

^c Clinicians and vaccination programs should screen for possible reactive airway diseases when considering use of LAIV for children ages 2–4 years, and should avoid use of this vaccine in children with asthma or a recent wheezing episode.

^d Live attenuated influenza vaccine coadministration has been evaluated systematically only among children ages 12-15 months who received measles, mumps, and rubella vaccine or varicella vaccine.

^e Inactivated influenza vaccine coadministration has been evaluated systematically only among adults who received pneumococcal polysaccharide or zoster vaccine.

- Individuals who have immune deficiencies such as HIV infection
- Individuals at high risk who should not be vaccinated or who want to avoid influenza illness⁴

Use of Antivirals in Conjunction With LAIV

The safety of consecutively administering LAIV and antiviral medications has not been studied. Because antivirals reduce the replication of influenza virus, it is advisable to wait at least 48 hours after completion of antiviral therapy before administering LAIV. Antivirals should not be administered until 2 weeks after administration of LAIV, and individuals who receive antivirals 12 days or less following LAIV administration should be revaccinated.⁴

Vaccination of Healthcare Professionals

On January 1, 2007, the Joint Commission on Accreditation of Healthcare Organizations approved an infection control standard that requires organizations it accredits to provide influenza vaccination to all staff, including volunteers and licensed independent healthcare professionals (HCPs) who have close patient contact.⁴

Vaccination of HCPs has been shown to reduce morbidity associated with influenza in healthcare settings and also has been associated with reduced work absenteeism. Yet, despite the benefits

Table 3. Recommended Daily Dosage of Influenza Antiviral Medications for Treatment and Chemoprophylaxis – United States

Antiviral Agent	Age Group (yrs)				
	1-6	7-9	10-12	13-64	≥65
Zanamivir					
Treatment, Influenza A & B	NA (2 inhalations) twice daily	10mg (2 inhalations) twice daily	10mg (2 inhalations) twice daily	10mg (2 inhalations) twice daily	10mg (2 inhalations) twice daily
	1-4	5-9			
Chemoprophylaxis¶, Influenza A & B	NA	10mg (2 inhalations) once daily	10mg (2 inhalations) once daily	10mg (2 inhalations) once daily	10mg (2 inhalations) once daily
Oseltamivir					
Treatment§, Influenza A & B	Dose varies by child's weight§§	Dose varies by child's weight§§	Dose varies by child's weight§§	75mg twice daily	75mg twice daily
Chemoprophylaxis, Influenza A & B	Dose varies by child's weight*	Dose varies by child's weight*	Dose varies by child's weight*	75mg once daily	75mg once daily

Zanamivir (Relenza® – inhaled powder – from GlaxoSmithKline) is approved for treatment of individuals 7 years and older and approved for chemoprophylaxis of individuals 5 years and older. Oseltamivir (Tamiflu – tablet – from Roche Pharmaceuticals) is approved for treatment or chemoprophylaxis of individuals 1 year and older. No antiviral medications are approved for treatment or chemoprophylaxis of influenza among children age <1 year. This information is based on data published by the Food and Drug Administration (FDA), which is available at <http://www.fda.gov>.

¶ Chemoprophylaxis is only required for the first 14 days after vaccination, if the vaccination is provided after the start of influenza season in the community.

§ A reduction in the dose of Oseltamivir is recommended for individuals with creatinine clearance <30mL/min.

§§ The treatment dosing recommendation for children who weigh <15 kg is 30 mg twice a day. For children who weigh >15-23 kg, the dose is 45 mg twice a day. For children who weigh >23-40 kg, the dose is 60 mg twice a day. For children who weigh >40 kg, the dose is 75 mg twice a day.

*The chemoprophylaxis dosing recommendation for children who weigh <15 kg is 30 mg once a day. For those who weigh >15-23 kg, the dose is 45 mg once a day. For children who weigh >23-40 kg, the dose is 60 mg once a day. For children who weigh >40 kg, the dose is 75 mg once a day.

From: Fiore AE, Shay DK, Haber P, et al. Prevention and Control of Influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008. *MMWR* 2007;56[No. RR-6].

nosuppressed for 7 days after receiving the vaccine.⁴

The optimal time to vaccinate HCPs is during October and November; however, offering vaccine throughout the influenza season also is recommended. Possible strategies for improving vaccination rates among HCPs include free vaccination, vaccination clinics, mobile vaccination carts, vaccination access during all shifts, and modeling and support by employers.⁷

Information on infection control for HCPs is available on the CDC Web site at <http://www.cdc.gov/flu/professionals/infectioncontrol/index.htm>.

Public Health and Clinical Tools to Assist in the Identification of Influenza

Rates of accurate diagnosis increase when epidemiologic data support the clinical suspicion of infection.¹⁰ Healthcare professionals who have current information about the influenza viruses and subtypes and strains currently circulating in their communities will be better equipped to recognize influenza symptoms and accurately diagnose cases of influenza. One tool available is the regularly updated information provided by local and state

vaccination confers, recent national survey data demonstrated a vaccination coverage level of only 42% among HCPs as recently as the 2005-2006 season. The Healthcare Infection Control Practices Advisory Committee and the ACIP recommend that HCPs who decline vaccination for reasons other than medical contraindications should be required to sign a declination form. A 2006 study of HCP vaccination in Wisconsin hospitals and nursing homes reported an association between the use of signed declination forms and significantly higher rates of vaccination.⁹

Healthcare professionals who are in close contact with individuals who have severely compromised immune systems should receive TIV. Likewise, HCPs who have severely compromised immune systems should avoid administering LAIV because of the increased risk of infection. Healthcare professionals who do receive LAIV should avoid contact with individuals who are immu-

health departments and the CDC. Each week from October through mid-May, the CDC provides an online update at <http://www.cdc.gov/flu/weekly/fluactivity.htm>.

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Understanding the life cycle of the influenza virus is vital to providing effective treatment. Influenza is spread primarily through droplets of respiratory secretion. Symptoms include abrupt onset of fever (37.7 °C to 40.0 °C [100 °F to 104 °F]), non-productive cough, sore throat, malaise, myalgia, rhinitis, and headache. Among children, additional symptoms may include nausea, otitis media, and vomiting.⁴ In elderly individuals, the skin may be hot, dry, or diaphoretic.¹⁰

The typical incubation period for influenza is 1 to 4 days. Adults shed influenza virus beginning the day before symptom onset and for as long as 5 to 10 days after illness onset; the amount of virus that is shed, however, decreases quickly by 3 to 5 days after onset. Young children also might shed virus several days before illness onset, and children can be infectious for >10 days after symptom onset. Hospitalized patients and individuals with severely compromised immune systems may shed influenza virus for weeks or months.⁴ Knowing when a patient is most contagious can aid healthcare professionals in advising patients to stay home and avoid contact with others.

Conclusion

Family physicians can help prevent the spread of influenza by staying abreast of current epidemiologic trends in their communities, recognizing the symptoms, and correctly diagnosing and treating the illness. Despite the availability of vaccine and the clinical evidence that annual vaccination is the most effective method for preventing influenza infection, vaccination rates in the United States are low. Vaccination, not only of patients, but also of those who care for patients, should be one of the highest priorities in family medicine. In those for whom vaccination is contraindicated, antiviral medications should be considered for influenza treatment and chemoprophylaxis.⁴

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Disclosure Statements: Dr. Temte, Dr. Campos-Outcalt, Ms. Gangel, and Ms. LaRocque have returned disclosure forms indicating that they have no financial interest in or affiliation with any commercial supporter or providers of any commercial services discussed in this educational material.

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CMEbulletin

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CME Bulletin is published by the American Academy of Family Physicians, 11400 Tomahawk Creek Parkway Leawood, Kansas 66211-2672 • www.aafp.org

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Self-Assessment Quiz

1. What percentage of the US population is covered by current recommendations for influenza vaccine?
A. 29%
B. 53%
C. 64%
D. 83%
2. Trivalent inactivated influenza vaccine is not indicated for:
A. Children between 24 and 59 months with a history of wheezing.
B. Individuals with anaphylactic hypersensitivity to eggs.
C. Pregnant women.
D. Individuals who are positive for human immunodeficiency virus.
3. What is the maximum interval between influenza symptom onset and initiation of oseltamivir or zanamivir therapy?
A. Within 12 hours.
B. Within 36 hours.
C. Within 48 hours.
D. Within 72 hours.
4. Which groups of healthcare professionals can safely be vaccinated with live attenuated influenza vaccine?
A. Healthy, nonpregnant and younger than 50 years.
B. Healthy and pregnant.
C. Those providing care for patients with severely compromised immune systems.
D. Any healthcare professionals.
5. Which statement is true regarding influenza?
A. Incubation period is 1-4 days.
B. Viral shedding decreases rapidly at 3-5 days after onset of symptoms.
C. Most individuals will fully recover within 1-2 weeks after symptom onset.
D. All the above.

Answers: 1. D; 2. B; 3. A; 4. A; 5. D

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Answers (Please circle one):

	A	B	C	D		5	4	3	2	1
1.	A	B	C	D	Relevance of topic to my practice	5	4	3	2	1
2.	A	B	C	D	Currency of clinical information	5	4	3	2	1
3.	A	B	C	D	Usefulness of clinical information	5	4	3	2	1
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