



# MMWR<sup>TM</sup>

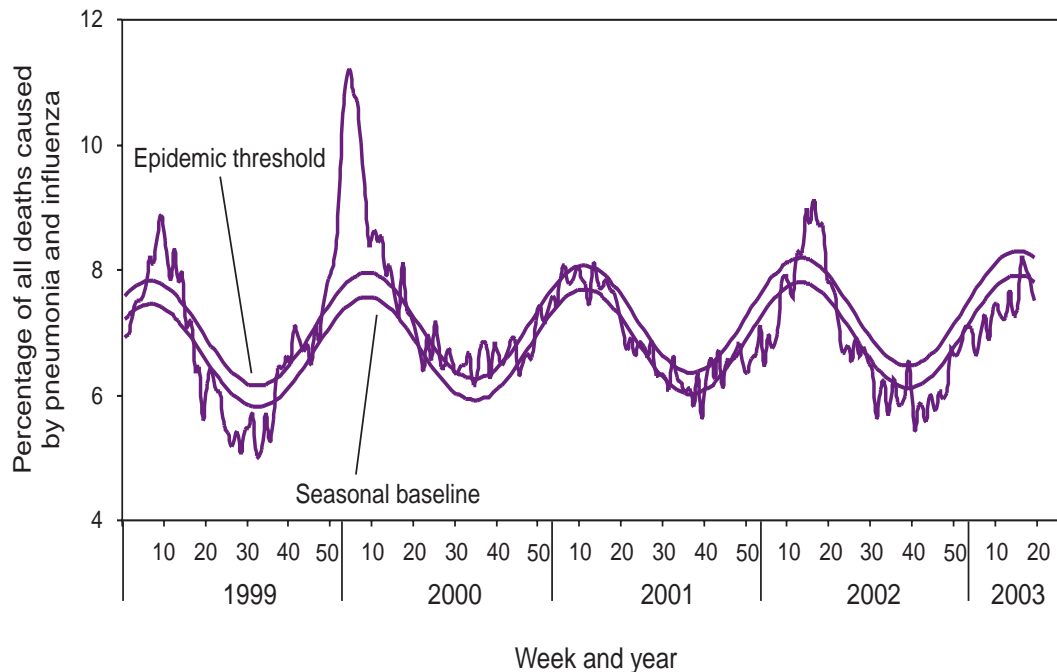
## Morbidity and Mortality Weekly Report

Recommendations and Reports

April 25, 2003 / Vol. 52 / No. RR-8

### Prevention and Control of Influenza

#### Recommendations of the Advisory Committee on Immunization Practices (ACIP)



**INSIDE: Continuing Education Examination**

The *MMWR* series of publications is published by the Epidemiology Program Office, Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services, Atlanta, GA 30333.

### SUGGESTED CITATION

Centers for Disease Control and Prevention. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2003;52(No. RR-8):[inclusive page numbers].

#### Centers for Disease Control and Prevention

Julie L. Gerberding, M.D., M.P.H.  
*Director*

David W. Fleming, M.D.  
*Deputy Director for Public Health Science*

Dixie E. Snider, Jr., M.D., M.P.H.  
*Associate Director for Science*

#### Epidemiology Program Office

Stephen B. Thacker, M.D., M.Sc.  
*Director*

#### Office of Scientific and Health Communications

John W. Ward, M.D.  
*Director*  
*Editor, MMWR Series*

Suzanne M. Hewitt, M.P.A.  
*Managing Editor, MMWR Series*

C. Kay Smith-Akin, M.Ed.  
*Lead Technical Writer/Editor*  
*Project Editor*

Beverly J. Holland  
*Lead Visual Information Specialist*

Lynda G. Cupell  
Malbea A. Heilman  
*Visual Information Specialists*

Quang M. Doan  
Erica R. Shaver  
*Information Technology Specialists*

**On the Cover:** The curve depicts the excess pneumonia and influenza deaths that were recorded in 122 cities during periods when influenza viruses were in circulation, 1999–2003.

## CONTENTS

Introduction .....	1
Primary Changes and Updates in the Recommendations ...	2
Influenza and Its Burden .....	2
Options for Controlling Influenza .....	3
Recommendations for Using Inactivated Influenza Vaccine ...	7
Target Groups for Vaccination .....	7
Additional Information Regarding Vaccination of Specific Populations .....	8
Persons Who Should Not Be Vaccinated with Inactivated Influenza Vaccine .....	11
Timing of Annual Vaccination with Inactivated Influenza Vaccine .....	11
Dosage .....	12
Inactivated Influenza Vaccine Use for Young Children, by Manufacturer .....	12
Route .....	12
Side Effects and Adverse Reactions .....	12
Simultaneous Administration of Other Vaccines, Including Childhood Vaccines .....	14
Strategies for Implementing These Recommendations in Health-Care Settings .....	14
Inactivated Influenza Vaccine Supply .....	16
Live, Attenuated Intranasal Influenza Vaccine .....	16
Recommendations for Using Antiviral Agents for Influenza .	16
Role of Laboratory Diagnosis .....	17
Indications for Use .....	17
Dosage .....	19
Route .....	22
Pharmacokinetics .....	22
Side Effects and Adverse Reactions .....	22
Use During Pregnancy .....	24
Drug Interactions .....	24
Antiviral Drug-Resistant Strains of Influenza .....	24
Sources of Information Regarding Influenza and Its Surveillance .....	25
Additional Information Regarding Influenza Infection Control Among Specific Populations .....	25
References .....	26

The preparers of this report have signed a conflict of interest disclosure form that verifies no conflict of interest.

# Prevention and Control of Influenza

## Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Prepared by

Carolyn B. Bridges, M.D.<sup>1</sup>

Scott A. Harper, M.D.<sup>1</sup>

Keiji Fukuda, M.D.<sup>1</sup>

Timothy M. Uyeki, M.D.<sup>1</sup>

Nancy J. Cox, Ph.D.<sup>1</sup>

James A. Singleton, M.S.<sup>2</sup>

<sup>1</sup>*Division of Viral and Rickettsial Diseases*

*National Center for Infectious Diseases*

<sup>2</sup>*Epidemiology and Surveillance Division*

*National Immunization Program*

### Summary

*This report updates the 2002 recommendations by the Advisory Committee on Immunization Practices (ACIP) on the use of influenza vaccine and antiviral agents (CDC. Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practices [ACIP]. MMWR 2002;51[No. RR-3]:1–31). The 2003 recommendations include new or updated information regarding 1) the timing of influenza vaccination by age and risk group; 2) influenza vaccine for children aged 6–23 months; 3) the 2003–2004 trivalent inactivated vaccine virus strains: A/Moscow/10/99 (H3N2)-like, A/New Caledonia/20/99 (H1N1)-like, and B/Hong Kong/330/2001-like antigens (for the A/Moscow/10/99 [H3N2]-like antigen, manufacturers will use the antigenically equivalent A/Panama/2007/99 [H3N2] virus, and for the B/Hong Kong/330/2001-like antigen, manufacturers will use either B/Hong Kong/330/2001 or the antigenically equivalent B/Hong Kong/1434/2002); 4) availability of certain influenza vaccine doses with reduced thimerosal content, including single 0.25 mL-dose syringes; and 5) manufacturers of influenza vaccine for the U.S. market. Although the optimal time to vaccinate against influenza is October and November, vaccination in December and later continues to be strongly recommended. A link to this report and other information regarding influenza can be accessed at <http://www.cdc.gov/ncidod/diseases/flu/fluvirus.htm>.*

### Introduction

Epidemics of influenza typically occur during the winter months and have been responsible for an average of approximately 36,000 deaths/year in the United States during 1990–1999 (1). Influenza viruses also can cause pandemics, during which rates of illness and death from influenza-related complications can increase dramatically worldwide. Influenza viruses cause disease among all age groups (2–4). Rates of infection are highest among children, but rates of serious illness and death are highest among persons aged  $\geq 65$  years and persons of any age who have medical conditions that place them at increased risk for complications from influenza (2,5–7).

Influenza vaccination is the primary method for preventing influenza and its severe complications. In this report from the Advisory Committee on Immunization Practices (ACIP), the primary target groups recommended for annual vaccination are 1) groups that are at increased risk for influenza-related complications (e.g., persons aged  $\geq 65$  years and persons of any age with certain chronic medical conditions); 2) the group aged 50–64 years because this group has an elevated prevalence of certain chronic medical conditions; and 3) persons who live with or care for persons at high risk (e.g., health-care workers and household contacts who have frequent contact with persons at high risk and who can transmit influenza to persons at high risk). Vaccination is associated with reductions in influenza-related respiratory illness and physician visits among all age groups, hospitalization and death among persons at high risk, otitis media among children, and work absenteeism among adults (8–18). Although influenza vaccination levels increased substantially during the 1990s, further improvements in vaccine coverage levels are needed, chiefly among persons aged  $< 65$  years who are at increased risk for influenza-related complications among all racial and ethnic

The material in this report originated in the National Center for Infectious Diseases, James M. Hughes, M.D., Director, and the Division of Viral and Rickettsial Diseases, James LeDuc, Ph.D., Director; and the National Immunization Program, Walter A. Orenstein, M.D., Director, and Epidemiology and Surveillance Division, Melinda Wharton, M.D., Director.

groups and among blacks and Hispanics aged  $\geq 65$  years. ACIP recommends using strategies to improve vaccination levels, including using reminder/recall systems and standing orders programs (19,20). Although influenza vaccination remains the cornerstone for the control and treatment of influenza, information is also presented regarding antiviral medications, because these agents are an adjunct to vaccine.

## Primary Changes and Updates in the Recommendations

The 2003 recommendations include five principal changes or updates:

1. The optimal time to receive influenza vaccine continues to be October and November. However, because of vaccine distribution delays during 2000–2002, ACIP recommends that vaccination efforts in October focus on persons aged  $\geq 50$  years and those aged 6–23 months, persons aged 2–49 years with certain medical conditions that place them at increased risk for influenza-related complications, children aged  $< 9$  years receiving influenza vaccine for the first time, health-care workers, and household contacts of persons at high risk, and that vaccination of other groups begin in November.
2. Because young, otherwise healthy children are at increased risk for influenza-related hospitalization, influenza vaccination of healthy children aged 6–23 months continues to be encouraged when feasible. Vaccination of children aged  $\geq 6$  months who have certain medical conditions continues to be strongly recommended.
3. The 2003–2004 trivalent inactivated vaccine virus strains are A/Moscow/10/99 (H3N2)-like, A/New Caledonia/20/99 (H1N1)-like, and B/Hong Kong/330/2001-like antigens (for the A/Moscow/10/99 [H3N2]-like antigen, manufacturers will use the antigenically equivalent A/Panama/2007/99 [H3N2] virus, and for the B/Hong Kong/330/2001-like antigen, manufacturers will use either B/Hong Kong/330/2001 or the antigenically equivalent B/Hong Kong/1434/2002).
4. A limited amount of influenza vaccine with reduced thimerosal content, including 0.25-mL single-dose syringe preparations for children aged 6–35 months, should be available for the 2003–04 influenza season.
5. Influenza vaccine for the U.S. market will be available from two manufacturers in 2003–04, compared with three manufacturers in 2002–03.

## Influenza and Its Burden

### Biology of Influenza

Influenza A and B are the two types of influenza viruses that cause epidemic human disease (21). Influenza A viruses are further categorized into subtypes on the basis of two surface antigens: hemagglutinin (H) and neuraminidase (N). Influenza B viruses are not categorized into subtypes. Since 1977, influenza A (H1N1) viruses, influenza A (H3N2) viruses, and influenza B viruses have been in global circulation. In 2001, influenza A (H1N2) viruses that probably emerged after genetic reassortment between human A (H3N2) and A (H1N1) viruses began circulating widely. Both influenza A and B viruses are further separated into groups on the basis of antigenic characteristics. New influenza virus variants result from frequent antigenic change (i.e., antigenic drift) resulting from point mutations that occur during viral replication. Influenza B viruses undergo antigenic drift less rapidly than influenza A viruses.

A person's immunity to the surface antigens, including hemagglutinin, reduces the likelihood of infection and severity of disease if infection occurs (22). Antibody against one influenza virus type or subtype confers limited or no protection against another. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype (23). Frequent development of antigenic variants through antigenic drift is the virologic basis for seasonal epidemics and the reason for the usual incorporation of  $\geq 1$  new strains in each year's influenza vaccine.

### Clinical Signs and Symptoms of Influenza

Influenza viruses are spread from person to person primarily through the coughing and sneezing of infected persons (21). The incubation period for influenza is 1–4 days, with an average of 2 days (24). Adults typically are infectious from the day before symptoms begin through approximately 5 days after illness onset. Children can be infectious for  $\geq 10$  days, and young children can shed virus for  $\leq 6$  days before their illness onset. Severely immunocompromised persons can shed virus for weeks or months (25–28).

Uncomplicated influenza illness is characterized by the abrupt onset of constitutional and respiratory signs and symptoms (e.g., fever, myalgia, headache, severe malaise, nonproductive cough, sore throat, and rhinitis) (29). Among children, otitis media, nausea, and vomiting are also commonly reported with influenza illness (30–32). Respiratory illness caused by

influenza is difficult to distinguish from illness caused by other respiratory pathogens on the basis of symptoms alone (see Role of Laboratory Diagnosis). Reported sensitivities and specificities of clinical definitions for influenza-like illness in studies primarily among adults that include fever and cough have ranged from 63% to 78% and 55% to 71%, respectively, compared with viral culture (33,34). Sensitivity and predictive value of clinical definitions can vary, depending on the degree of co-circulation of other respiratory pathogens and the level of influenza activity (35). A study among older nonhospitalized patients determined that symptoms of fever, cough, and acute onset had a positive predictive value of 30% for influenza (36), whereas a study of hospitalized older patients with chronic cardiopulmonary disease determined that a combination of fever, cough, and illness of <7 days was 78% sensitive and 73% specific for influenza (37). However, a study among vaccinated older persons with chronic lung disease reported that cough was not predictive of influenza infection, although having a fever or feverishness was 68% sensitive and 54% specific for influenza infection (38).

Influenza illness typically resolves after a limited number of days for the majority of persons, although cough and malaise can persist for >2 weeks. Among certain persons, influenza can exacerbate underlying medical conditions (e.g., pulmonary or cardiac disease), lead to secondary bacterial pneumonia or primary influenza viral pneumonia, or occur as part of a coinfection with other viral or bacterial pathogens (39). Young children with influenza infection can have initial symptoms mimicking bacterial sepsis with high fevers (40,41), and ≤20% of children hospitalized with influenza can have febrile seizures (31,42). Influenza infection has also been associated with encephalopathy, transverse myelitis, Reye syndrome, myositis, myocarditis, and pericarditis (31,39,43,44).

### Hospitalizations and Deaths from Influenza

The risks for complications, hospitalizations, and deaths from influenza are higher among persons aged ≥65 years, young children, and persons of any age with certain underlying health conditions (see Persons at Increased Risk for Complications) than among healthy older children and younger adults (1,6,8,45–50). Estimated rates of influenza-associated hospitalizations have varied substantially by age group in studies conducted during different influenza epidemics (Table 1).

Among children aged 0–4 years, hospitalization rates have ranged from approximately 500/100,000 population for those with high-risk medical conditions to 100/100,000 population for those without high-risk medical conditions (51–54). Within the 0–4 age group, hospitalization rates are highest

among children aged 0–1 years and are comparable to rates reported among persons ≥65 years (53,54) (Table 1).

During influenza epidemics from 1969–70 through 1994–95, the estimated overall number of influenza-associated hospitalizations in the United States ranged from approximately 16,000 to 220,000/epidemic. An average of approximately 114,000 influenza-related excess hospitalizations occurred per year, with 57% of all hospitalizations occurring among persons aged <65 years. Since the 1968 influenza A (H3N2) virus pandemic, the greatest numbers of influenza-associated hospitalizations have occurred during epidemics caused by type A (H3N2) viruses, with an estimated average of 142,000 influenza-associated hospitalizations per year (55).

Influenza-related deaths can result from pneumonia as well as from exacerbations of cardiopulmonary conditions and other chronic diseases. Older adults account for ≥90% of deaths attributed to pneumonia and influenza (1,50). In a recent study of influenza epidemics, approximately 19,000 influenza-associated pulmonary and circulatory deaths per influenza season occurred during 1976–1990, compared with approximately 36,000 deaths during 1990–1999 (1). Estimated rates of influenza-associated pulmonary and circulatory deaths/100,000 persons were 0.4–0.6 among persons aged 0–49 years, 7.5 among persons aged 50–64 years, and 98.3 among persons aged ≥65 years. In the United States, the number of influenza-associated deaths might be increasing in part because the number of older persons is increasing (56). In addition, influenza seasons in which influenza A (H3N2) viruses predominate are associated with higher mortality (57); influenza A (H3N2) viruses predominated in 90% of influenza seasons from 1990–1999, compared with 57% of seasons from 1976–1990 (1).

### Options for Controlling Influenza

In the United States, the primary option for reducing the effect of influenza is immunoprophylaxis with inactivated (i.e., killed virus) vaccine (see Recommendations for Using Inactivated Influenza Vaccine). Vaccinating persons at high risk for complications each year before seasonal increases in influenza virus circulation is the most effective means of reducing the effect of influenza. Vaccination coverage can be increased by administering vaccine to persons during hospitalizations or routine health-care visits before the influenza season, making special visits to physicians' offices or clinics unnecessary. When vaccine and epidemic strains are well-matched, achieving increased vaccination rates among persons living in closed settings (e.g., nursing homes and other chronic-care facilities)



TABLE 1. Estimated rates of influenza-associated hospitalization by age group and risk group from selected studies.\*

Study years	Population	Age Group	Hospitalizations/ 100,000 persons with high-risk conditions	Hospitalizations/ 100,000 persons without high-risk conditions
1973–1993†§	Tennessee	0–11 mos	1,900	496–1,038¶
1973–1993§**	Medicaid	1–2 yrs	800	186
		3–4 yrs	320	86
		5–14 yrs	92	41
1992–1997†† §§	Two Health Maintenance Organizations	0–23 mos		144–187
		2–4 yrs		0–25
		5–17 yrs		8–12
1968–1969, 1970–1971, 1972–1973¶¶ ***	Health Maintenance Organization	15–44 yrs	56–110	23–25
		45–64 yrs	392–635	13–23
		≥65 yrs	399–518	—
1969–1995††† ***	National Hospital Discharge Data	<65 yrs	—	20–42§§§ ¶¶¶
		≥65 yrs	—	125–228¶¶¶

\* Rates were estimated in years and populations with low vaccination rates. Hospitalization rates can be expected to decrease as vaccination rates increase. Vaccination can be expected to reduce influenza-related hospitalizations by 30%–70% among older persons and likely by even higher percentages among younger age groups when vaccine and circulating influenza virus strains are antigenically similar.

† **Source:** Neuzil KM, Mellen BG, Wright PF, Mitchel EF, Griffin MR. Effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. *New Engl J Med* 2000;342:225–31.

§ Outcomes were for acute cardiac or pulmonary conditions.

¶ The low estimate is for infants aged 6–11 months, and the high estimate is for infants aged 0–5 months.

\*\* **Source:** Neuzil KM, Wright PF, Mitchel EF, Griffin MR. Burden of influenza illness in children with asthma and other chronic medical conditions. *J Pediatr* 2000;137:856–64.

†† **Source:** Izurieta HS, Thompson WW, Kramarz P, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. *New Engl J Med* 2000;342:232–9.

§§ Outcomes were for acute pulmonary conditions. Influenza-attributable hospitalization rates for children at high risk were not included in this study.

¶¶ **Source:** Barker WH, Mullooly JP. Impact of epidemic type A influenza in a defined adult population. *Am J Epidemiol* 1980;112:798–811.

\*\*\* Outcomes were limited to hospitalizations in which either pneumonia or influenza was listed as the first condition on discharge records (Simonsen) or included anywhere in the list of discharge diagnoses (Barker).

††† **Source:** Simonsen L, Fukuda, K, Schonberger LB, Cox NJ. Impact of influenza epidemics on hospitalizations. *J Infect Dis* 2000;181:831–7.

§§§ Persons at high risk and not at high risk for influenza-related complications are combined.

¶¶¶ The low estimate is the average during influenza A(H1N1) or influenza B-predominate seasons, and the high estimate is the average during influenza A(H3N2)-predominate seasons.

and among staff can reduce the risk for outbreaks by inducing herd immunity (13). Vaccination of health-care workers and other persons in close contact with persons at increased risk for severe influenza illness can also reduce transmission of influenza and subsequent influenza-related complications. Antiviral drugs used for chemoprophylaxis or treatment of influenza are a key adjunct to vaccine (see Recommendations for Using Antiviral Agents for Influenza). However, antiviral medications are not a substitute for vaccination.

### Inactivated Influenza Vaccine Composition

Inactivated influenza vaccines are standardized to contain the hemagglutinins of strains (i.e., typically two type A and one type B), representing the influenza viruses likely to circulate in the United States in the upcoming winter. The vaccine is made from highly purified, egg-grown viruses that have been

made noninfectious (i.e., inactivated or killed) (58). Subvirion and purified surface antigen preparations are available. Because the vaccine viruses are initially grown in embryonated hens' eggs, the vaccine might contain limited amounts of residual egg protein.

Manufacturing processes differ by manufacturer. Manufacturers might use different compounds to inactivate influenza viruses and add antibiotics to prevent bacterial contamination. Package inserts should be consulted for additional information.

Inactivated influenza vaccine distributed in the United States might also contain thimerosal, a mercury-containing compound, as the preservative (59,60). Thimerosal has been used as a preservative in vaccines since the 1930s. Although no evidence of harm caused by low levels of thimerosal in vaccines

has been reported, in 1999, the U.S. Public Health Service and other organizations recommended that efforts be made to reduce the thimerosal content in vaccines to decrease total mercury exposure, chiefly among infants and pregnant woman (59,61). Since mid-2001, routinely administered, noninfluenza childhood vaccines for the U.S. market have been manufactured either without or with only trace amounts of thimerosal to provide a substantial reduction in the total mercury exposure from vaccines for children (62).

For the 2003–04 influenza season, a limited number of individually packaged doses (i.e., single-dose syringes) of preservative-free influenza vaccine (<1 mcg mercury/0.5 mL dose) will be available, including single-dose vaccine packaged in doses of 0.5 mL (dose for persons aged  $\geq 3$  years) and 0.25 mL (dose for children 6–35 months). Reduced thimerosal-content vaccine is available both from Evans Vaccines, Ltd. (FDA-approved for persons aged  $\geq 4$  years) and from Aventis Pasteur (FDA-approved for persons aged  $\geq 6$  months) (see Inactivated Influenza Vaccine Use For Young Children, By Manufacturer). Multidose vials and single-dose syringes of influenza vaccine containing approximately 25 mcg thimerosal/0.5 mL dose are also available, as they have been in previous years. Because of the known risks of severe illness from influenza infection and the benefits of vaccination and because a substantial safety margin has been incorporated into the health guidance values for organic mercury exposure, the benefit of influenza vaccine with reduced or standard thimerosal content outweighs the theoretical risk, if any, from thimerosal (59,63). The removal of thimerosal from other vaccines further reduces the theoretical risk from thimerosal in influenza vaccines.

The trivalent inactivated influenza vaccine prepared for the 2003–04 season will include A/Moscow/10/99 (H3N2)-like, A/New Caledonia/20/99 (H1N1)-like, and B/Hong Kong/330/2001-like antigens. For the A/Moscow/10/99 (H3N2)-like antigen, manufacturers will use the antigenically equivalent A/Panama/2007/99 (H3N2) virus, and for the B/Hong Kong/330/2001-like antigen, manufacturers will use either B/Hong Kong/330/2001 or the antigenically equivalent B/Hong Kong/1434/2002. These viruses will be used because of their growth properties and because they are representative of influenza viruses likely to circulate in the United States during the 2003–04 influenza season. Because circulating influenza A (H1N2) viruses are a reassortant of influenza A (H1N1) and (H3N2) viruses, antibody directed against influenza A (H1N1) and influenza (H3N2) vaccine strains will provide protection against circulating influenza A (H1N2) viruses.

## Effectiveness of Inactivated Influenza Vaccine

The effectiveness of influenza vaccine depends primarily on the age and immunocompetence of the vaccine recipient and the degree of similarity between the viruses in the vaccine and those in circulation. The majority of vaccinated children and young adults develop high postvaccination hemagglutination inhibition antibody titers (64–66). These antibody titers are protective against illness caused by strains similar to those in the vaccine (65–68).

**Adults Aged <65 Years.** When the vaccine and circulating viruses are antigenically similar, influenza vaccine prevents influenza illness in approximately 70%–90% of healthy adults aged <65 years (9,12,69,70). Vaccination of healthy adults also has resulted in decreased work absenteeism and decreased use of health-care resources, including use of antibiotics, when the vaccine and circulating viruses are well-matched (9–12,70,71).

**Children.** Children aged as young as 6 months can develop protective levels of antibody after influenza vaccination (64,65,72–75), although the antibody response among children at high risk of influenza-related complications might be lower than among healthy children (76,77). In a randomized study among children aged 1–15 years, inactivated influenza vaccine was 77%–91% effective against influenza respiratory illness and was 44%–49%, 74%–76%, and 70%–81% effective against influenza seroconversion among children aged 1–5, 6–10, and 11–15 years, respectively (66). One study (78) reported a vaccine efficacy of 56% against influenza illness among healthy children aged 3–9 years and another study (79) determined vaccine efficacy of 22%–54% and 60%–78% among children with asthma aged 2–6 years and 7–14 years, respectively. A 2-year randomized study of children aged 6–24 months determined that  $\geq 89\%$  of children seroconverted to all three vaccine strains during both years (80). During year 1, among 411 children, vaccine efficacy was 66% (95% confidence interval [CI] = 34% and 82%) against culture-confirmed influenza (attack rates: 5.5% and 15.9% among vaccine and placebo groups). During year 2, among 375 children, vaccine efficacy was –7% (95% CI = –247% and 67%; attack rates: 3.6% and 3.3% among vaccine and placebo groups). However, no overall reduction in otitis media was reported (80). Other studies report that trivalent inactivated influenza vaccine decreases the incidence of influenza-associated otitis media among young children by approximately 30% (16,17).

**Adults Aged  $\geq 65$  years of Age.** Older persons and persons with certain chronic diseases might develop lower postvaccination antibody titers than healthy young adults and thus can remain susceptible to influenza-related upper respiratory tract infection (81–83). A randomized trial among noninstitutionalized persons aged  $\geq 60$  years reported a vaccine efficacy of 58% against influenza respiratory illness, but indicated that efficacy might be lower among those aged  $\geq 70$  years (84). The vaccine can also be effective in preventing secondary complications and reducing the risk for influenza-related hospitalization and death among adults  $\geq 65$  years with and without high-risk medical conditions (e.g., heart disease and diabetes) (13–15,18,85). Among elderly persons living outside of nursing homes or similar chronic-care facilities, influenza vaccine is 30%–70% effective in preventing hospitalization for pneumonia and influenza (15,86). Among elderly persons residing in nursing homes, influenza vaccine is most effective in preventing severe illness, secondary complications, and deaths. Among this population, the vaccine can be 50%–60% effective in preventing hospitalization or pneumonia and 80% effective in preventing death, although the effectiveness in preventing influenza illness often ranges from 30% to 40% (87–89).

### Cost-Effectiveness of Influenza Vaccine

Influenza vaccination can reduce both health-care costs and productivity losses associated with influenza illness. Economic studies of influenza vaccination of persons aged  $\geq 65$  years conducted in the United States have reported overall societal cost savings and substantial reductions in hospitalization and death (15,86,90). Studies of adults aged  $< 65$  years have reported that vaccination can reduce both direct medical costs and indirect costs from work absenteeism (8,10–12,70,91). Reductions of 34%–44% in physician visits, 32%–45% in lost workdays (10,12), and 25% in antibiotic use for influenza-associated illnesses have been reported (12). One cost-effectiveness analysis estimated a cost of approximately \$60–\$4,000/illness averted among healthy persons aged 18–64 years, depending on the cost of vaccination, the influenza attack rate, and vaccine effectiveness against influenza-like illness (70). Another cost-benefit economic model estimated an average annual savings of \$13.66/person vaccinated (92). In the second study, 78% of all costs prevented were costs from lost work productivity, whereas the first study did not include productivity losses from influenza illness. Economic studies specifically evaluating the cost-effectiveness of vaccinating persons aged 50–64 years are not available, and the number of studies that examine the economics of routinely vaccinating children are limited (8,93–95). However, in a study that included all age groups, cost utility improved with increasing

age and among those with chronic medical conditions (8). Among persons aged  $\geq 65$  years, vaccination resulted in a net savings per quality-adjusted life year (QALY) gained and resulted in costs of \$23–\$256/QALY among younger age groups. Additional studies of the relative cost-effectiveness and cost utility of influenza vaccination among children and among adults aged  $< 65$  years are needed and should be designed to account for year-to-year variations in influenza attack rates, illness severity, and vaccine efficacy when evaluating the long-term costs and benefits of annual vaccination.

### Vaccination Coverage Levels

Among persons aged  $\geq 65$  years, influenza vaccination levels increased from 33% in 1989 (96) to 66% in 1999 (97), surpassing the *Healthy People 2000* objective of 60% (98). Vaccine coverage reached the highest levels recorded (68%) during the 1999–00 influenza season, using the percentage of adults reporting influenza vaccination during the past 12 months who participated in the National Health Interview Survey (NHIS) during the first and second quarters of each calendar year as a proxy measure of influenza vaccine coverage for the previous influenza season (97). Possible reasons for the increase in influenza vaccination levels among persons aged  $\geq 65$  years through the 1999–00 influenza season include 1) greater acceptance of preventive medical services by practitioners; 2) increased delivery and administration of vaccine by health-care providers and sources other than physicians; 3) new information regarding influenza vaccine effectiveness, cost-effectiveness, and safety; and 4) the initiation of Medicare reimbursement for influenza vaccination in 1993 (8,14,15,87,88,99,100). Vaccine coverage increased more rapidly through the mid-1990s than during subsequent seasons (average annual percentage increase of 4% from 1988–89 to 1996–97 versus 1% from 1996–97 to 1999–00).

Estimated influenza vaccination coverage for the 2000–01 influenza season was lower than for the previous season among adults aged  $\geq 65$  years (64% versus 68%) and adults aged 50–64 years (32% versus 38%) (97). Delays in influenza vaccine supply during fall 2000 probably contributed to these declines in vaccination levels (see Inactivated Influenza Vaccine Supply). Estimated vaccine coverage for the 2001–02 season, during which less severe influenza vaccine supply delays occurred, were equivalent to 1999–00 season estimates (67% for adults aged  $\geq 65$  years and 35% for adults aged 50–64 years). Continued annual monitoring is needed to determine the effects of vaccine supply delays and other factors on vaccination coverage among persons aged  $\geq 50$  years. The *Healthy People 2010* objective is to achieve vaccination coverage for 90% of persons aged  $\geq 65$  years (101).



Reducing racial and ethnic health disparities, including disparities in vaccination coverage, is an overarching national goal (101). Although estimated influenza vaccination coverage for the 1999–00 season reached the highest levels recorded among older black, Hispanic, and white populations, vaccination levels among blacks and Hispanics continue to lag behind those among whites (97,102). Estimated influenza vaccination levels for the 2001–02 season among persons aged  $\geq 65$  years were 70% among non-Hispanic whites, 52% among non-Hispanic blacks, and 47% among Hispanics (97). Additional strategies are needed to achieve the *Healthy People 2010* objective among all racial and ethnic groups.

In 1997 and 1998, vaccination coverage estimates among nursing home residents were 64%–82% and 83%, respectively (103,104). The *Healthy People 2010* goal is to achieve influenza vaccination of 90% of nursing home residents, an increase from the *Healthy People 2000* goal of 80% (98,101).

For the 2000–01 influenza season, the estimated vaccination coverage among adults aged 18–64 years with high-risk conditions was 29%, substantially lower than the *Healthy People 2000* and *2010* objective of 60% (unpublished data, National Immunization Program [NIP], CDC, 2003) (98,101). Among persons aged 50–64 years, 41% of those with chronic medical conditions and 29% of those without chronic medical conditions received influenza vaccine. Only 21% of adults aged <50 years with high-risk conditions were vaccinated.

Reported vaccination levels are low among children at increased risk for influenza complications. One study conducted among patients in health maintenance organizations reported influenza vaccination percentages ranging from 9% to 10% among children with asthma (105). A 25% vaccination level was reported among children with severe to moderate asthma who attended an allergy and immunology clinic (106). However, a study conducted in a pediatric clinic demonstrated an increase in the vaccination percentage of children with asthma or reactive airways disease from 5% to 32% after implementing a reminder/recall system (107). One study reported 79% vaccination coverage among children attending a cystic fibrosis treatment center (108). Increasing vaccination coverage among persons who have high-risk conditions and are aged <65 years, including children at high risk, is the highest priority for expanding influenza vaccine use.

Annual vaccination is recommended for health-care workers. Nonetheless, NHIS reported vaccination coverage of only 34% and 36% among health-care workers in the 1997 and 2001 surveys, respectively (109) (unpublished NHIS data, NIP, CDC, 2003). Vaccination of health-care workers has been associated with reduced work absenteeism (9) and fewer deaths among nursing home patients (110,111).

Limited information is available regarding using influenza vaccine among pregnant women. Among women aged 18–44 years without diabetes responding to the 2001 Behavioral Risk Factor Surveillance System, those reporting they were pregnant were less likely to report influenza vaccination during the past 12 months (13.7%) than those not pregnant (16.8%) (112). However, vaccination coverage was slightly higher than in 1997 when 11.2% of pregnant and 14.4% of nonpregnant women were vaccinated. Similar results were determined by using the 1997–2001 NHIS data, excluding pregnant women who reported diabetes, heart disease, lung disease, and other selected high-risk conditions (unpublished NHIS data, NIP, CDC, 2002). Although not directly measuring influenza vaccination among women who were past the first trimester of pregnancy during influenza season, these data indicate low compliance with the ACIP recommendations for pregnant women. In a study of influenza vaccine acceptance by pregnant women, 71% who were offered the vaccine chose to be vaccinated (113). However, a 1999 survey of obstetricians and gynecologists determined that only 39% administered influenza vaccine to obstetric patients, although 86% agreed that pregnant women's risk for influenza-related morbidity and mortality increases during the last two trimesters (114).

## Recommendations for Using Inactivated Influenza Vaccine

Influenza vaccine is strongly recommended for any person aged  $\geq 6$  months who is at increased risk for complications from influenza. In addition, health-care workers and other persons (including household members) in close contact with persons at high risk should be vaccinated to decrease the risk for transmitting influenza to persons at high risk. Influenza vaccine also can be administered to any person aged  $\geq 6$  months to reduce the chance of becoming infected with influenza.

### Target Groups for Vaccination

#### Persons at Increased Risk for Complications

Vaccination is recommended for the following persons who are at increased risk for complications from influenza:

- persons aged  $\geq 65$  years;
- residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions;
- adults and children who have chronic disorders of the pulmonary or cardiovascular systems, including asthma;
- adults and children who have required regular medical follow-up or hospitalization during the preceding year

because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus [HIV]);

- children and adolescents (aged 6 months–18 years) who are receiving long-term aspirin therapy and, therefore, might be at risk for experiencing Reye syndrome after influenza infection; and
- women who will be in the second or third trimester of pregnancy during the influenza season.

In 2000, approximately 73 million persons in the United States fell into  $\geq 1$  of these target groups, including 35 million persons aged  $\geq 65$  years; and 12 million adults aged 50–64 years, 18 million adults aged 18–49 years, and 8 million children aged 6 months–17 years with  $\geq 1$  medical conditions that are associated with an increased risk for influenza-related complications (115).

### Persons Aged 50–64 Years

Vaccination is recommended for persons aged 50–64 years because this group has an increased prevalence of persons with high-risk conditions. In 2000, approximately 42 million persons in the United States were aged 50–64 years, of whom 12 million (29%) had  $\geq 1$  high-risk medical conditions (115). Influenza vaccine has been recommended for this entire age group to increase the low vaccination rates among persons in this age group with high-risk conditions. Age-based strategies are more successful in increasing vaccine coverage than patient-selection strategies based on medical conditions. Persons aged 50–64 years without high-risk conditions also receive benefit from vaccination in the form of decreased rates of influenza illness, decreased work absenteeism, and decreased need for medical visits and medication, including antibiotics (9–12). Further, 50 years is an age when other preventive services begin and when routine assessment of vaccination and other preventive services has been recommended (116,117).

### Persons Who Can Transmit Influenza to Those at High Risk

Persons who are clinically or subclinically infected can transmit influenza virus to persons at high risk for complications from influenza. Decreasing transmission of influenza from caregivers and household contacts to persons at high risk might reduce influenza-related deaths among persons at high risk. Evidence from two studies indicates that vaccination of health-care personnel is associated with decreased deaths among nursing home patients (110,111). Vaccination of health-care personnel and others in close contact with persons at high risk, including household contacts, is recommended.

The following groups should be vaccinated:

- physicians, nurses, and other personnel in both hospital and outpatient-care settings, including medical emergency response workers (e.g., paramedics and emergency medical technicians);
- employees of nursing homes and chronic-care facilities who have contact with patients or residents;
- employees of assisted living and other residences for persons in groups at high risk;
- persons who provide home care to persons in groups at high risk; and
- household contacts (including children) of persons in groups at high risk.

In addition, because children aged 0–23 months are at increased risk for influenza-related hospitalization (52–54), vaccination is encouraged for their household contacts and out-of-home caregivers, particularly for contacts of children aged 0–5 months because influenza vaccines have not been approved by the U.S. Food and Drug Administration (FDA) for use among children aged  $< 6$  months (see Healthy Young Children).

## Additional Information Regarding Vaccination of Specific Populations

### Pregnant Women

Influenza-associated excess deaths among pregnant women were documented during the pandemics of 1918–19 and 1957–58 (118–121). Case reports and limited studies also indicate that pregnancy can increase the risk for serious medical complications of influenza (122–126). An increased risk might result from increases in heart rate, stroke volume, and oxygen consumption; decreases in lung capacity; and changes in immunologic function during pregnancy. A study of the impact of influenza during 17 interpandemic influenza seasons demonstrated that the relative risk for hospitalization for selected cardiorespiratory conditions among pregnant women enrolled in Medicaid increased from 1.4 during weeks 14–20 of gestation to 4.7 during weeks 37–42, in comparison with women who were 1–6 months postpartum (127). Women in their third trimester of pregnancy were hospitalized at a rate (i.e., 250/100,000 pregnant women) comparable with that of nonpregnant women who had high-risk medical conditions. Researchers estimated that an average of 1–2 hospitalizations could be prevented for every 1,000 pregnant women vaccinated.

Because of the increased risk for influenza-related complications, women who will be beyond the first trimester of pregnancy ( $> 14$  weeks gestation) during the influenza season should

be vaccinated. Certain providers prefer to administer influenza vaccine during the second trimester to avoid a coincidental association with spontaneous abortion, which is common in the first trimester, and because exposures to vaccines traditionally have been avoided during the first trimester (128). Pregnant women who have medical conditions that increase their risk for complications from influenza should be vaccinated before the influenza season, regardless of the stage of pregnancy. A study of influenza vaccination of >2,000 pregnant women demonstrated no adverse fetal effects associated with influenza vaccine (129). However, additional data are needed to confirm the safety of vaccination during pregnancy.

The majority of influenza vaccine distributed in the United States contains thimerosal, a mercury-containing compound, as a preservative, but influenza vaccine with reduced thimerosal content is available in limited quantities (see Inactivated Influenza Vaccine Composition). Thimerosal has been used in U.S. vaccines since the 1930s. No data or evidence exists of any harm caused by the level of mercury exposure that might occur from influenza vaccination. Because pregnant women are at increased risk for influenza-related complications and because a substantial safety margin has been incorporated into the health guidance values for organic mercury exposure, the benefit of influenza vaccine with reduced or standard thimerosal content outweighs the potential risk, if any, for thimerosal (59,63).

### Persons Infected with HIV

Limited information is available regarding the frequency and severity of influenza illness or the benefits of influenza vaccination among persons with HIV infection (130,131). However, a retrospective study of young and middle-aged women enrolled in Tennessee's Medicaid program determined that the attributable risk for cardiopulmonary hospitalizations among women with HIV infection was higher during influenza seasons than during the peri-influenza periods. The risk for hospitalization was higher for HIV-infected women than for women with other well-recognized high-risk conditions, including chronic heart and lung diseases (132). Another study estimated that the risk for influenza-related death was 9.4–14.6/10,000 persons with acquired immunodeficiency syndrome (AIDS) compared with 0.09–0.10/10,000 among all persons aged 25–54 years and 6.4–7.0/10,000 among persons aged ≥65 years (133). Other reports demonstrate that influenza symptoms might be prolonged and the risk for complications from influenza increased for certain HIV-infected persons (134–136).

Influenza vaccination has been demonstrated to produce substantial antibody titers against influenza among vaccinated

HIV-infected persons who have minimal AIDS-related symptoms and high CD4<sup>+</sup> T-lymphocyte cell counts (137–140). A limited, randomized, placebo-controlled trial determined that influenza vaccine was highly effective in preventing symptomatic, laboratory-confirmed influenza infection among HIV-infected persons with a mean of 400 CD4<sup>+</sup> T-lymphocyte cells/mm<sup>3</sup>; a limited number of persons with CD4<sup>+</sup> T-lymphocyte cell counts of <200 were included in that study (131). A nonrandomized study among HIV-infected persons determined that influenza vaccination was most effective among persons with >100 CD4<sup>+</sup> cells and among those with <30,000 viral copies of HIV type-1/mL (136). Among persons who have advanced HIV disease and low CD4<sup>+</sup> T-lymphocyte cell counts, influenza vaccine might not induce protective antibody titers (139,140); a second dose of vaccine does not improve the immune response in these persons (140,141).

One study determined that HIV RNA levels increased transiently in one HIV-infected person after influenza infection (142). Studies have demonstrated a transient (i.e., 2–4 week) increase in replication of HIV-1 in the plasma or peripheral blood mononuclear cells of HIV-infected persons after vaccine administration (139,143). Other studies using similar laboratory techniques have not documented a substantial increase in the replication of HIV (144–147). Deterioration of CD4<sup>+</sup> T-lymphocyte cell counts or progression of HIV disease have not been demonstrated among HIV-infected persons after influenza vaccination compared with unvaccinated persons (140,148). Limited information is available concerning the effect of antiretroviral therapy on increases in HIV RNA levels after either natural influenza infection or influenza vaccination (130,149). Because influenza can result in serious illness and because influenza vaccination can result in the production of protective antibody titers, vaccination will benefit HIV-infected persons, including HIV-infected pregnant women.

### Breastfeeding Mothers

Influenza vaccine does not affect the safety of mothers who are breastfeeding or their infants. Breastfeeding does not adversely affect the immune response and is not a contraindication for vaccination.

### Travelers

The risk for exposure to influenza during travel depends on the time of year and destination. In the tropics, influenza can occur throughout the year. In the temperate regions of the Southern Hemisphere, the majority of influenza activity occurs during April–September. In temperate climate zones

of the Northern and Southern Hemispheres, travelers also can be exposed to influenza during the summer, especially when traveling as part of large organized tourist groups (e.g., on cruise ships) that include persons from areas of the world where influenza viruses are circulating (150,151). Persons at high risk for complications of influenza who were not vaccinated with influenza vaccine during the preceding fall or winter should consider receiving influenza vaccine before travel if they plan to

- travel to the tropics;
- travel with organized tourist groups at any time of year; or
- travel to the Southern Hemisphere during April–September.

No information is available regarding the benefits of revaccinating persons before summer travel who were already vaccinated in the preceding fall. Persons at high risk who received the previous season's vaccine before travel should be revaccinated with the current vaccine in the following fall or winter. Persons aged  $\geq 50$  years and others at high risk might want to consult with their physicians before embarking on travel during the summer to discuss the symptoms and risks for influenza and the advisability of carrying antiviral medications for either prophylaxis or treatment of influenza.

### Healthy Young Children

Studies indicate that rates of hospitalization are higher among young children than older children when influenza viruses are in circulation (51–53,152,153). The increased rates of hospitalization are comparable with rates for other groups considered at high risk for influenza-related complications. However, the interpretation of these findings has been confounded by co-circulation of respiratory syncytial viruses, which are a cause of serious respiratory viral illness among children and which frequently circulate during the same time as influenza viruses (154–156). Two recent studies have attempted to separate the effects of respiratory syncytial viruses and influenza viruses on rates of hospitalization among children who do not have high-risk conditions (52,53). Both studies reported that otherwise healthy children aged  $< 2$  years, and possibly children aged 2–4 years, are at increased risk for influenza-related hospitalization compared with older healthy children (Table 1). Among the Tennessee Medicaid population during 1973–1993, healthy children aged 6 months– $< 3$  years had rates of influenza-associated hospitalization comparable with or higher than rates among children aged 3–14 years with high-risk conditions (Table 1) (52,54). Another Tennessee study reported a

hospitalization rate of 3–4/1,000 healthy children aged  $< 2$  years/year for laboratory-confirmed influenza (32).

Because children aged 6–23 months are at substantially increased risk for influenza-related hospitalizations, ACIP, the American Academy of Pediatrics, and the American Academy of Family Physicians continue to encourage vaccination of all children in this age group when feasible (157). However, the benefits of a full recommendation to vaccinate all children aged 6–23 months will depend on the identification and implementation of practical and efficient annual influenza vaccination strategies for providers of health care to children. In the interim, the identification of potential strategies for influenza vaccination of children, review of additional data from ongoing studies among children aged 6–23 months receiving influenza vaccine, and efforts to educate parents and providers regarding the impact of influenza and the potential benefits and risks of vaccinating young children will continue. A full recommendation might be made within a year. ACIP continues to strongly recommend influenza vaccination of persons aged  $\geq 6$  months who have high-risk medical conditions.

The current inactivated influenza vaccine is not approved by FDA for use among children aged  $< 6$  months, the pediatric group at greatest risk for influenza-related complications (52). Vaccinating their household contacts and out-of-home caregivers might decrease the probability of influenza among these children.

Beginning in March 2003, the group of children eligible for influenza vaccine coverage under the Vaccines for Children (VFC) program was expanded to include all VFC-eligible children aged 6–23 months and VFC-eligible children aged 2–18 years who are household contacts of children aged 0–23 months (158).

### General Population

In addition to the groups for which annual influenza vaccination is recommended, physicians should administer influenza vaccine to any person who wishes to reduce the likelihood of becoming ill with influenza (the vaccine can be administered to children  $\geq 6$  months), depending on vaccine availability (see Inactivated Influenza Vaccine Supply). Persons who provide essential community services should be considered for vaccination to minimize disruption of essential activities during influenza outbreaks. Students or other persons in institutional settings (e.g., those who reside in dormitories) should be encouraged to receive vaccine to minimize the disruption of routine activities during epidemics.



## Persons Who Should Not Be Vaccinated with Inactivated Influenza Vaccine

Inactivated influenza vaccine should not be administered to persons known to have anaphylactic hypersensitivity to eggs or to other components of the influenza vaccine without first consulting a physician (see Side Effects and Adverse Reactions). Prophylactic use of antiviral agents is an option for preventing influenza among such persons. However, persons who have a history of anaphylactic hypersensitivity to vaccine components but who are also at high risk for complications from influenza can benefit from vaccine after appropriate allergy evaluation and desensitization. Information regarding vaccine components is located in package inserts from each manufacturer. Persons with acute febrile illness usually should not be vaccinated until their symptoms have abated. However, minor illnesses with or without fever do not contraindicate the use of influenza vaccine, particularly among children with mild upper respiratory tract infection or allergic rhinitis.

## Timing of Annual Vaccination with Inactivated Influenza Vaccine

The annual supply of inactivated influenza vaccine and the timing of its distribution cannot be guaranteed in any year. Information regarding the supply of 2003–04 vaccine might not be available until late summer or early fall 2003.

To allow vaccine providers to plan for the upcoming vaccination season, taking into account the yearly possibility of vaccine delays or shortages and the need to ensure vaccination of persons at high risk and their contacts, the ACIP recommends that vaccine campaigns conducted in October should focus their efforts primarily on persons at increased risk for influenza complications and their contacts, including health-care workers. Campaigns conducted in November and later should continue to vaccinate persons at high risk and their contacts, but also vaccinate other persons who wish to decrease their risk for influenza infection. Vaccination efforts for all groups should continue into December and beyond.

## Vaccination in October and November

The optimal time to vaccinate is usually during October–November. ACIP recommends that vaccine providers focus their vaccination efforts in October and earlier primarily on persons aged  $\geq 50$ , persons aged  $< 50$  years at increased risk of influenza-related complications (including children aged 6–23 months), household contacts of

persons at high risk (including out-of-home caregivers and household contacts of children aged 0–23 months), and health-care workers. Vaccination of children aged  $< 9$  years who are receiving vaccine for the first time should also begin in October because those persons need a booster dose 1 month after the initial dose. Efforts to vaccinate other persons who wish to decrease their risk for influenza infection should begin in November; however, if such persons request vaccination in October, vaccination should not be deferred. Materials to assist providers in prioritizing early vaccine are available at <http://www.cdc.gov/nip/flu/Provider.htm> (for information regarding vaccination of travelers, see the travelers section in this report).

## Timing of Organized Vaccination Campaigns

Persons planning substantial organized vaccination campaigns should consider scheduling these events after mid-October because the availability of vaccine in any location cannot be ensured consistently in the early fall. Scheduling campaigns after mid-October will minimize the need for cancellations because vaccine is unavailable. Campaigns conducted before November should focus efforts on vaccination of persons aged  $\geq 50$  years, persons aged  $< 50$  years at increased risk of influenza-related complications (including children aged 6–23 months), health-care workers, and household contacts of persons at high-risk (including children aged 0–23 months) to the extent feasible.

## Vaccination in December and Later

After November, certain persons who should or want to receive influenza vaccine remain unvaccinated. In addition, substantial amounts of vaccine have remained unused during the past three influenza seasons. To improve vaccine coverage, influenza vaccine should continue to be offered in December and throughout the influenza season as long as vaccine supplies are available, even after influenza activity has been documented in the community. In the United States, seasonal influenza activity can begin to increase as early as November or December, but influenza activity has not reached peak levels in the majority of recent seasons until late December–early March (Table 2). Therefore, although the timing of influenza

**TABLE 2. Month of peak influenza activity\* during 26 influenza seasons — United States, 1976–2002**

Month	December	January	February	March	April	May
Number (%) of years with peak influenza activity	4 (15)	6 (23)	11 (42)	3 (12)	1 (4)	1 (4)

\*The peak week of activity was defined as the week with the greatest percentage of respiratory specimens testing positive for influenza on the basis of a 3-week moving average. Laboratory data were provided by U.S. World Health Organization Collaborating Laboratories (unpublished data, National Center for Infectious Diseases, CDC).

activity can vary by region, vaccine administered after November is likely to be beneficial in the majority of influenza seasons. Adults develop peak antibody protection against influenza infection 2 weeks after vaccination (159,160).

### Vaccination Before October

To avoid missed opportunities for vaccination of persons at high risk for serious complications, such persons should be offered vaccine beginning in September during routine health-care visits or during hospitalizations, if vaccine is available. In facilities housing older persons (e.g., nursing homes), vaccination before October typically should be avoided because antibody levels in such persons can begin to decline within a limited time after vaccination (161).

### Dosage

Dosage recommendations vary according to age group (Table 3). Among previously unvaccinated children aged <9 years, two doses administered  $\geq 1$  month apart are recommended for satisfactory antibody responses. If possible, the second dose should be administered before December. Among adults, studies have indicated limited or no improvement in antibody response when a second dose is administered during the same season (162–164). Even when the current influenza vaccine contains  $\geq 1$  antigens administered in previous years,

**TABLE 3. Influenza vaccine\* dosage, by age group — United States, 2002–03 season**

Age group†	Dose	Number of doses	Route§
6–35 mos	0.25 mL	1 or 2¶	Intramuscular
3–8 yrs	0.50 mL	1 or 2¶	Intramuscular
$\geq 9$ yrs	0.50 mL	1	Intramuscular

\* Contains 15 mg each of A/Moscow/10/99 (H3N2)-like, A/New Caledonia/20/99 (H1N1)-like, and B/Hong Kong/330/2001-like antigens. For the A/Moscow/10/99 (H3N2)-like antigen, manufacturers will use the antigenically equivalent A/Panama/2007/99 (H3N2) virus. For the B/Hong Kong/330/2001-like antigen, manufacturers will use either B/Hong Kong/330/2001 or the antigenically equivalent B/Hong Kong/1434/2002. Manufacturers include Aventis Pasteur, Inc. (Fluzone® split); Evans Vaccines, Ltd. (Fluvirin™ purified surface antigen vaccine). Fluzone is Food and Drug Administration-approved for use among persons aged  $\geq 6$  months. Fluvirin is approved for use among persons aged  $\geq 4$  years. For further product information, call Aventis Pasteur at 800-822-2463, or Evans Vaccine, Ltd., at 800-200-4278.

† Because of their decreased potential for causing febrile reactions, only split-virus vaccines should be used for children aged <13 years. Split-virus vaccine might be labeled as split, subvirion, or purified-surface-antigen vaccine. Immunogenicity and side effects of split- and whole-virus vaccines are similar among adults when vaccines are administered at the recommended dosage. Whole-virus vaccine is not available in the United States.

§ For adults and older children, the recommended site of vaccination is the deltoid muscle. The preferred site for infants and young children is the anterolateral aspect of the thigh.

¶ Two doses administered  $\geq 1$  month apart are recommended for children aged <9 years who are receiving influenza vaccine for the first time.

annual vaccination with the current vaccine is necessary because immunity declines during the year after vaccination (165,166). Vaccine prepared for a previous influenza season should not be administered to provide protection for the current season.

### Inactivated Influenza Vaccine Use for Young Children, by Manufacturer

When vaccinating children aged 6 months–3 years, providers should use inactivated influenza vaccine that has been approved by FDA for this age group. Influenza vaccine from Aventis Pasteur, Inc., (Fluzone® split-virus) is approved for use among persons aged  $\geq 6$  months. Influenza vaccine from Evans Vaccines Ltd. (Fluvirin®) is labeled in the United States for use only among persons aged  $\geq 4$  years because data to demonstrate efficacy among younger persons have not been provided to FDA.

### Route

The intramuscular route is recommended for influenza vaccine. Adults and older children should be vaccinated in the deltoid muscle. A needle length  $\geq 1$  inches can be considered for these age groups because needles <1 inch might be of insufficient length to penetrate muscle tissue in certain adults and older children (167).

Infants and young children should be vaccinated in the anterolateral aspect of the thigh (62). ACIP recommends a needle length of 7/8–1 inch for children aged <12 months for intramuscular vaccination into the anterolateral thigh. When injecting into the deltoid muscle among children with adequate deltoid muscle mass, a needle length of 7/8–1¼ inches is recommended (62).

### Side Effects and Adverse Reactions

When educating patients regarding potential side effects, clinicians should emphasize that 1) inactivated influenza vaccine contains noninfectious killed viruses and cannot cause influenza; and 2) coincidental respiratory disease unrelated to influenza vaccination can occur after vaccination.

### Local Reactions

In placebo-controlled studies among adults, the most frequent side effect of vaccination is soreness at the vaccination site (affecting 10%–64% of patients) that lasts <2 days (12,168–170). These local reactions typically are mild and rarely interfere with the person's ability to conduct usual daily activities. One blinded, randomized, cross-over study among

1,952 adults and children with asthma, demonstrated that only body aches were reported more frequently after inactivated influenza vaccine (25.1%) than placebo-injection (20.8%) (171). One study (77) reported 20%–28% of asthmatic children aged 9 months–18 years with local pain and swelling and another study (75) reported 23% of children aged 6 months–4 years with chronic heart or lung disease had local reactions. A different study (74) reported no difference in local reactions among 53 children aged 6 months–6 years with high-risk medical conditions or among 305 healthy children aged 3–12 years in a placebo-controlled trial of inactivated influenza vaccine. In a study of 12 children aged 5–32 months, no substantial local or systemic reactions were noted (172).

### Systemic Reactions

Fever, malaise, myalgia, and other systemic symptoms can occur after vaccination and most often affect persons who have had no prior exposure to the influenza virus antigens in the vaccine (e.g., young children) (173,174). These reactions begin 6–12 hours after vaccination and can persist for 1–2 days. Recent placebo-controlled trials demonstrate that among older persons and healthy young adults, administration of split-virus influenza vaccine is not associated with higher rates of systemic symptoms (e.g., fever, malaise, myalgia, and headache) when compared with placebo injections (12,168–170).

Less information from published studies is available for children, compared with adults. However, in a randomized crossover study among both children and adults with asthma, no increase in asthma exacerbations was reported for either age group (171). An analysis of 215,600 children aged <18 years and 8,476 children aged 6–23 months enrolled in 1 of 5 health maintenance organizations reported no increase in biologically plausible medically attended events during the 2 weeks after inactivated influenza vaccination, compared with control periods 3–4 weeks before and after vaccination (175). In a study of 791 healthy children (66), postvaccination fever was noted among 11.5% of children aged 1–5 years, 4.6% among children aged 6–10 years, and 5.1% among children aged 11–15 years. Among children with high-risk medical conditions, one study of 52 children aged 6 months–4 years reported fever among 27% and irritability and insomnia among 25% (75); and a study among 33 children aged 6–18 months reported that one child had irritability and one had a fever and seizure after vaccination (176). No placebo comparison was made in these studies. However, in pediatric trials of A/New Jersey/76 swine influenza vaccine, no difference was reported between placebo and split-virus vaccine groups in febrile reactions after injection, although the vaccine was associated with mild local tenderness or erythema (74).

Limited data regarding potential adverse events after influenza vaccination are available from the Vaccine Adverse Event Reporting System (VAERS). During January 1, 1991–January 23, 2003, VAERS received 1,072 reports of adverse events among children aged <18 years, including 174 reports of adverse events among children aged 6–23 months. The number of influenza vaccine doses received by children during this time period is unknown. The most frequently reported events among children were fever, injection-site reactions, and rash (unpublished data, CDC, 2003). Because of the limitations of spontaneous reporting systems, determining causality for specific types of adverse events, with the exception of injection-site reactions, is usually not possible by using VAERS data alone.

Immediate — presumably allergic — reactions (e.g., hives, angioedema, allergic asthma, and systemic anaphylaxis) rarely occur after influenza vaccination (177). These reactions probably result from hypersensitivity to certain vaccine components; the majority of reactions probably are caused by residual egg protein. Although current influenza vaccines contain only a limited quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Persons who have had hives or swelling of the lips or tongue, or who have experienced acute respiratory distress or collapse after eating eggs should consult a physician for appropriate evaluation to help determine if vaccine should be administered. Persons who have documented immunoglobulin E (IgE)-mediated hypersensitivity to eggs, including those who have had occupational asthma or other allergic responses to egg protein, might also be at increased risk for allergic reactions to influenza vaccine, and consultation with a physician should be considered. Protocols have been published for safely administering influenza vaccine to persons with egg allergies (178–180).

Hypersensitivity reactions to any vaccine component can occur. Although exposure to vaccines containing thimerosal can lead to induction of hypersensitivity, the majority of patients do not have reactions to thimerosal when it is administered as a component of vaccines, even when patch or intradermal tests for thimerosal indicate hypersensitivity (181,182). When reported, hypersensitivity to thimerosal usually has consisted of local, delayed type hypersensitivity reactions (181).

### Guillain-Barré Syndrome

The 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré syndrome (GBS) (183,184). Among persons who received the swine influenza vaccine in 1976, the rate of GBS that exceeded the background rate was <10 cases/1 million persons vaccinated with the risk



for influenza vaccine-associated GBS higher among persons aged  $\geq 25$  years than persons  $< 25$  years (183). Evidence for a causal relation of GBS with subsequent vaccines prepared from other influenza viruses is unclear. Obtaining strong epidemiologic evidence for a possible limited increase in risk is difficult for such a rare condition as GBS, which has an annual incidence of 10–20 cases/1 million adults (185), and stretches the limits of epidemiologic investigation. More definitive data probably will require using other methodologies (e.g., laboratory studies of the pathophysiology of GBS).

During three of four influenza seasons studied during 1977–1991, the overall relative risk estimates for GBS after influenza vaccination were slightly elevated but were not statistically significant in any of these studies (186–188). However, in a study of the 1992–93 and 1993–94 seasons, the overall relative risk for GBS was 1.7 (95% CI = 1.0–2.8;  $p = 0.04$ ) during the 6 weeks after vaccination, representing approximately 1 additional case of GBS/1 million persons vaccinated. The combined number of GBS cases peaked 2 weeks after vaccination (189). Thus, investigations to date indicate no substantial increase in GBS associated with influenza vaccines (other than the swine influenza vaccine in 1976), and that, if influenza vaccine does pose a risk, it is probably slightly more than one additional case/1 million persons vaccinated. Cases of GBS after influenza infection have been reported, but no epidemiologic studies have documented such an association (190,191). Substantial evidence exists that multiple infectious illnesses, most notably *Campylobacter jejuni*, as well as upper respiratory tract infections are associated with GBS (185,192–194).

Even if GBS were a true side effect of vaccination in the years after 1976, the estimated risk for GBS of approximately 1 additional case/1 million persons vaccinated is substantially less than the risk for severe influenza, which could be prevented by vaccination among all age groups, especially persons aged  $\geq 65$  years and those who have medical indications for influenza vaccination (Table 1) (see Hospitalizations and Deaths from Influenza). The potential benefits of influenza vaccination in preventing serious illness, hospitalization, and death substantially outweigh the possible risks for experiencing vaccine-associated GBS. The average case fatality ratio for GBS is 6% and increases with age (185,195). No evidence indicates that the case fatality ratio for GBS differs among vaccinated persons and those not vaccinated.

The incidence of GBS among the general population is low, but persons with a history of GBS have a substantially greater likelihood of subsequently experiencing GBS than persons without such a history (186,196). Thus, the likelihood of coincidentally experiencing GBS after influenza vaccination is

expected to be greater among persons with a history of GBS than among persons with no history of this syndrome. Whether influenza vaccination specifically might increase the risk for recurrence of GBS is unknown; therefore, avoiding vaccinating persons who are not at high risk for severe influenza complications and who are known to have experienced GBS within 6 weeks after a previous influenza vaccination is prudent. As an alternative, physicians might consider using influenza antiviral chemoprophylaxis for these persons. Although data are limited, for the majority of persons who have a history of GBS and who are at high risk for severe complications from influenza, the established benefits of influenza vaccination justify yearly vaccination.

### Simultaneous Administration of Other Vaccines, Including Childhood Vaccines

Adult target groups for influenza and pneumococcal polysaccharide vaccination overlap considerably (197). For persons at high risk who have not previously been vaccinated with pneumococcal vaccine, health-care providers should strongly consider administering pneumococcal polysaccharide and inactivated influenza vaccines concurrently. Both vaccines can be administered at the same time at different sites without increasing side effects (198,199). However, influenza vaccine is administered each year, whereas pneumococcal vaccine is not. A patient's verbal history is acceptable for determining prior pneumococcal vaccination status. When indicated, pneumococcal vaccine should be administered to patients who are uncertain regarding their vaccination history (197).

No studies regarding the simultaneous administration of inactivated influenza vaccine and other childhood vaccines have been conducted. However, inactivated vaccines usually do not interfere with the immune response to other inactivated or live vaccines (62) and children at high risk for influenza-related complications, including those aged 6–23 months, can receive influenza vaccine at the same time they receive other routine vaccinations.

### Strategies for Implementing These Recommendations in Health-Care Settings

Successful vaccination programs combine publicity and education for health-care workers and other potential vaccine recipients, a plan for identifying persons at high risk, use of reminder/recall systems, and efforts to remove administrative and financial barriers that prevent persons from receiving the vaccine, including use of standing orders programs (19,200).



Using standing orders programs is recommended for long-term care facilities (e.g., nursing homes and skilled nursing facilities), hospitals, and home health agencies to ensure the administration of recommended vaccinations for adults (201). Standing orders programs for both influenza and pneumococcal vaccination should be conducted under the supervision of a licensed practitioner according to a physician-approved facility or agency policy by health-care personnel trained to screen patients for contraindications to vaccination, to administer vaccine, and to monitor for adverse events. A rule from the Centers for Medicare and Medicaid Services (CMS) recently removed the physician signature requirement for the administration of influenza and pneumococcal vaccines to Medicare and Medicaid patients in hospitals, long-term care facilities, and home health agencies (201). To the extent allowed by local and state law, these facilities and agencies may implement standing orders for influenza and pneumococcal vaccination of Medicare- and Medicaid-eligible patients. Other settings (e.g., outpatient facilities, managed care organizations, assisted living facilities, correctional facilities, pharmacies, and adult workplaces) are encouraged to introduce standing orders programs as well (20). Persons for whom influenza vaccine is recommended can be identified and vaccinated in the settings described in the following sections.

### **Outpatient Facilities Providing Ongoing Care**

Staff in facilities providing ongoing medical care (e.g., physicians' offices, public health clinics, employee health clinics, hemodialysis centers, hospital specialty-care clinics, and outpatient rehabilitation programs) should identify and label the medical records of patients who should receive vaccination. Vaccine should be offered during visits beginning in September and throughout the influenza season. The offer of vaccination and its receipt or refusal should be documented in the medical record. Patients for whom vaccination is recommended who do not have regularly scheduled visits during the fall should be reminded by mail, telephone, or other means of the need for vaccination.

### **Outpatient Facilities Providing Episodic or Acute Care**

Beginning each September, acute health-care facilities (e.g., emergency rooms and walk-in clinics) should offer vaccinations to persons for whom vaccination is recommended or provide written information regarding why, where, and how to obtain the vaccine. This written information should be available in languages appropriate for the populations served by the facility.

### **Nursing Homes and Other Residential Long-Term Care Facilities**

During October and November each year, vaccination should be routinely provided to all residents of chronic-care facilities with the concurrence of attending physicians. Consent for vaccination should be obtained from the resident or a family member at the time of admission to the facility or any time afterwards. All residents should be vaccinated at one time, preceding the influenza season. Residents admitted through March after completion of the facility's vaccination program should be vaccinated at the time of admission.

### **Acute-Care Hospitals**

Persons of all ages (including children) with high-risk conditions and persons aged  $\geq 50$  years who are hospitalized at any time during September–March should be offered and strongly encouraged to receive influenza vaccine before they are discharged. In one study, 39%–46% of patients hospitalized during the winter with influenza-related diagnoses had been hospitalized during the preceding autumn (202). Thus, the hospital serves as a setting in which persons at increased risk for subsequent hospitalization can be identified and vaccinated. However, vaccination of persons at high risk during or after their hospitalizations is often not done. In a study of hospitalized Medicare patients, only 31.6% were vaccinated before admission, 1.9% during admission, and 10.6% after admission (203). Using standing orders in hospitals increases vaccination rates among hospitalized persons (204).

### **Visiting Nurses and Others Providing Home Care to Persons at High Risk**

Beginning in September, nursing care plans should identify patients for whom vaccination is recommended, and vaccine should be administered in the home, if necessary. Caregivers and other persons in the household (including children) should be referred for vaccination.

### **Other Facilities Providing Services to Persons Aged $\geq 50$ Years**

Beginning in October, such facilities as assisted living housing, retirement communities, and recreation centers should offer unvaccinated residents and attendees vaccination on-site before the influenza season. Staff education should emphasize the need for influenza vaccine.

### **Health-Care Personnel**

Beginning in October each year, health-care facilities should offer influenza vaccinations to all personnel, including night

and weekend staff. Particular emphasis should be placed on providing vaccinations for persons who care for members of groups at high risk. Efforts should be made to educate health-care personnel regarding the benefits of vaccination and the potential health consequences of influenza illness for themselves and their patients. Measures should be taken to provide all health-care personnel convenient access to influenza vaccine at the work site, free of charge, as part of employee health programs.

## Inactivated Influenza Vaccine Supply

In 2000, difficulties with growing and processing the influenza A (H3N2) vaccine strain and other manufacturing problems resulted in substantial delays in distribution of 2000–01 influenza vaccine, and fewer vaccine doses were available than had been distributed in 1999 (205). In 2001, a less severe delay occurred, although, by December 2001, approximately 87.7 million doses of vaccine were produced, more than in any year except the 1976–77 swine influenza vaccine campaign (206,207). During 2002, approximately 95 million doses were produced by the end of November, and approximately 12 million doses remained unsold by the vaccine manufacturers. For 2003, only two companies will be producing influenza vaccine for the U.S. market (Aventis Pasteur, Inc., and Evans Vaccines, Ltd.), in comparison with 2002, when three companies manufactured influenza vaccine for the U.S. market.

Influenza vaccine delivery delays or vaccine shortages remain possible in part because of the inherent critical time constraints in manufacturing the vaccine given the annual updating of the influenza vaccine strains. Steps being taken to address possible future delays or vaccine shortages include identification and implementation of ways to expand the influenza vaccine supply, improvement of targeted delivery of vaccine to groups at high risk when delays or shortages are expected, and encouragement of the continued administration of vaccine beyond November and throughout the influenza season (December–March) every year (see Timing of Annual Vaccination with Inactivated Influenza Vaccine).

## Live, Attenuated Intranasal Influenza Vaccine

Intranasally administered, cold-adapted, live, attenuated, influenza virus vaccines (LAIVs) are being used in Russia and have been under development in the United States since the 1960s (208–212). LAIVs have been studied as monovalent, bivalent, and trivalent formulations (211,212). LAIVs consist of live viruses that replicate in the upper respiratory tract, that

induce minimal symptoms (i.e., are attenuated), and that replicate poorly at temperatures in the lower respiratory tract (i.e., are temperature-sensitive). Possible advantages of LAIVs are their potential to induce a broad mucosal and systemic immune response, their ease of administration, and the acceptability of an intranasal rather than intramuscular route of administration. In a 5-year study that compared trivalent inactivated vaccine and bivalent LAIVs (administered by nose drops) and that used related but different vaccine strains, the two vaccines were determined to be approximately equivalent in terms of effectiveness (66,213). In a 1996–97 study of children aged 15–71 months, an intranasally administered trivalent LAIV was 93% effective in preventing culture-positive influenza A (H3N2) and B infections, reduced febrile otitis media among vaccinated children by 30%, and reduced otitis media with concomitant antibiotic use by 35% compared with unvaccinated children (214). In a follow-up study during the 1997–98 season, the trivalent LAIV was 86% effective in preventing culture-positive influenza among children, despite a suboptimal match between the vaccine's influenza A (H3N2) component and the predominant circulating influenza A (H3N2) virus (215). A study conducted among healthy adults during the same season reported a 9%–24% reduction in febrile respiratory illnesses and 13%–28% reduction in lost work days (216). No study has directly compared the efficacy or effectiveness of trivalent inactivated vaccine and trivalent LAIV. An application for licensure of a LAIV is under review by FDA.

## Recommendations for Using Antiviral Agents for Influenza

Antiviral drugs for influenza are an adjunct to influenza vaccine for controlling and preventing influenza. However, these agents are not a substitute for vaccination. Four licensed influenza antiviral agents are available in the United States: amantadine, rimantadine, zanamivir, and oseltamivir.

Amantadine and rimantadine are chemically related antiviral drugs known as adamantanes with activity against influenza A viruses but not influenza B viruses. Amantadine was approved in 1966 for chemoprophylaxis of influenza A (H2N2) infection and was later approved in 1976 for the treatment and chemoprophylaxis of influenza type A virus infections among adults and children aged  $\geq 1$  years. Rimantadine was approved in 1993 for treatment and chemoprophylaxis of influenza A infection among adults and prophylaxis among children. Although rimantadine is approved only for chemoprophylaxis of influenza A infection among children, certain

specialists in the management of influenza consider it appropriate for treatment of influenza A among children (217).

Zanamivir and oseltamivir are chemically related antiviral drugs known as neuraminidase inhibitors and that have activity against both influenza A and B viruses. Both zanamivir and oseltamivir were approved in 1999 for treating uncomplicated influenza infections. Zanamivir is approved for treating persons aged  $\geq 7$  years, and oseltamivir is approved for treatment for persons aged  $\geq 1$  years. In 2000, oseltamivir was approved for chemoprophylaxis of influenza among persons aged  $\geq 13$  years.

The four drugs differ in terms of their pharmacokinetics, side effects, routes of administration, approved age groups, dosages, and costs. An overview of the indications, use, administration, and known primary side effects of these medications is presented in the following sections. Information contained in this report might not represent FDA approval or approved labeling for the antiviral agents described. Package inserts should be consulted for additional information.

## Role of Laboratory Diagnosis

Appropriate treatment of patients with respiratory illness depends on accurate and timely diagnosis. The early diagnosis of influenza can reduce the inappropriate use of antibiotics and provide the option of using antiviral therapy. However, because certain bacterial infections can produce symptoms similar to influenza, bacterial infections should be considered and appropriately treated, if suspected. In addition, bacterial infections can occur as a complication of influenza.

Influenza surveillance information as well as diagnostic testing can aid clinical judgment and help guide treatment decisions. The accuracy of clinical diagnosis of influenza on the basis of symptoms alone is limited because symptoms from illness caused by other pathogens can overlap considerably with influenza (29,33,34). Influenza surveillance by state and local health departments and CDC can provide information regarding the presence of influenza viruses in the community. Surveillance can also identify the predominant circulating types, subtypes, and strains of influenza.

Diagnostic tests available for influenza include viral culture, serology, rapid antigen testing, polymerase chain reaction (PCR) and immunofluorescence (24). Sensitivity and specificity of any test for influenza might vary by the laboratory that performs the test, the type of test used, and the type of specimen tested. Among respiratory specimens for viral isolation or rapid detection, nasopharyngeal specimens are typically more effective than throat swab specimens (218). As with any diagnostic test, results should be evaluated in the context of other clinical information available to the physician.

Commercial rapid diagnostic tests are available that can be used by laboratories in outpatient settings to detect influenza viruses within 30 minutes (24,219). These rapid tests differ in the types of influenza viruses they can detect and whether they can distinguish between influenza types. Different tests can detect 1) only influenza A viruses; 2) both influenza A and B viruses, but not distinguish between the two types; or 3) both influenza A and B and distinguish between the two. The types of specimens acceptable for use (i.e., throat swab, nasal wash, or nasal swab) also vary by test. The specificity and, in particular, the sensitivity of rapid tests are lower than for viral culture and vary by test (220,221). Because of the lower sensitivity of the rapid tests, physicians should consider confirming negative tests with viral culture or other means. Further, when interpreting results of a rapid influenza test, physicians should consider the positive and negative predictive values of the test in the context of the level of influenza activity in their community. Package inserts and the laboratory performing the test should be consulted for more details regarding use of rapid diagnostic tests. Additional information concerning diagnostic testing is located at [http://www.cdc.gov/ncidod/diseases/flu/flu\\_dx\\_table.htm](http://www.cdc.gov/ncidod/diseases/flu/flu_dx_table.htm).

Despite the availability of rapid diagnostic tests, collecting clinical specimens for viral culture is critical, because only culture isolates can provide specific information regarding circulating influenza subtypes and strains. This information is needed to compare current circulating influenza strains with vaccine strains, to guide decisions regarding influenza treatment and chemoprophylaxis, and to formulate vaccine for the coming year. Virus isolates also are needed to monitor the emergence of antiviral resistance and the emergence of novel influenza A subtypes that might pose a pandemic threat.

## Indications for Use

### Treatment

When administered within 2 days of illness onset to otherwise healthy adults, amantadine and rimantadine can reduce the duration of uncomplicated influenza A illness, and zanamivir and oseltamivir can reduce the duration of uncomplicated influenza A and B illness by approximately 1 day, compared with placebo (70,222–236). More clinical data are available concerning the efficacy of zanamivir and oseltamivir for treatment of influenza A infection than for treatment of influenza B infection (224–235,237–240). However, *in vitro* data and studies of treatment among mice and ferrets (241–248), in addition to clinical studies have documented that zanamivir and oseltamivir have activity against influenza B viruses (228,232–234,239,240).

None of the four antiviral agents has been demonstrated to be effective in preventing serious influenza-related complications (e.g., bacterial or viral pneumonia or exacerbation of chronic diseases). Evidence for the effectiveness of these four antiviral drugs is based principally on studies of patients with uncomplicated influenza (249). Data are limited and inconclusive concerning the effectiveness of amantadine, rimantadine, zanamivir, and oseltamivir for treatment of influenza among persons at high risk for serious complications of influenza (27,222,224,225,227,228,235,250–254). Fewer studies of the efficacy of influenza antivirals have been conducted among pediatric populations, compared with adults (222,225,231,232,251,255,256). One study of oseltamivir treatment documented a decreased incidence of otitis media among children (232). Inadequate data exist regarding the safety and efficacy of any of the influenza antiviral drugs for use among children aged <1 year (221).

To reduce the emergence of antiviral drug-resistant viruses, amantadine or rimantadine therapy for persons with influenza A illness should be discontinued as soon as clinically warranted, typically after 3–5 days of treatment or within 24–48 hours after the disappearance of signs and symptoms. The recommended duration of treatment with either zanamivir or oseltamivir is 5 days.

### Chemoprophylaxis

Chemoprophylactic drugs are not a substitute for vaccination, although they are critical adjuncts in the prevention and control of influenza. Both amantadine and rimantadine are indicated for the chemoprophylaxis of influenza A infection, but not influenza B. Both drugs are approximately 70%–90% effective in preventing illness from influenza A infection (70,222,251). When used as prophylaxis, these antiviral agents can prevent illness while permitting subclinical infection and development of protective antibody against circulating influenza viruses. Therefore, certain persons who take these drugs will develop protective immune responses to circulating influenza viruses. Amantadine and rimantadine do not interfere with the antibody response to the vaccine (222). Both drugs have been studied extensively among nursing home populations as a component of influenza outbreak-control programs, which can limit the spread of influenza within chronic care institutions (222,250,257–259).

Among the neuraminidase inhibitor antivirals, zanamivir and oseltamivir, only oseltamivir has been approved for prophylaxis, but community studies of healthy adults indicate that both drugs are similarly effective in preventing febrile, laboratory-confirmed influenza illness (efficacy: zanamivir, 84%; oseltamivir, 82%) (260–262). Both antiviral agents have also been reported to prevent influenza illness among persons

administered chemoprophylaxis after a household member was diagnosed with influenza (239,262,263). Experience with prophylactic use of these agents in institutional settings or among patients with chronic medical conditions is limited in comparison with the adamantanes (234,253,254,264–266). One 6-week study of oseltamivir prophylaxis among nursing home residents reported a 92% reduction in influenza illness (234,267). Use of zanamivir has not been reported to impair the immunologic response to influenza vaccine (233,268). Data are not available regarding the efficacy of any of the four antiviral agents in preventing influenza among severely immunocompromised persons.

When determining the timing and duration for administering influenza antiviral medications for prophylaxis, factors related to cost, compliance, and potential side effects should be considered. To be maximally effective as prophylaxis, the drug must be taken each day for the duration of influenza activity in the community. However, to be most cost-effective, one study of amantadine or rimantadine prophylaxis reported that the drugs should be taken only during the period of peak influenza activity in a community (269).

**Persons at High Risk Who Are Vaccinated After Influenza Activity Has Begun.** Persons at high risk for complications of influenza still can be vaccinated after an outbreak of influenza has begun in a community. However, the development of antibodies in adults after vaccination takes approximately 2 weeks (159,160). When influenza vaccine is administered while influenza viruses are circulating, chemoprophylaxis should be considered for persons at high risk during the time from vaccination until immunity has developed. Children aged <9 years who receive influenza vaccine for the first time can require 6 weeks of prophylaxis (i.e., prophylaxis for 4 weeks after the first dose of vaccine and an additional 2 weeks of prophylaxis after the second dose).

**Persons Who Provide Care to Those at High Risk.** To reduce the spread of virus to persons at high risk during community or institutional outbreaks, chemoprophylaxis during peak influenza activity can be considered for unvaccinated persons who have frequent contact with persons at high risk. Persons with frequent contact include employees of hospitals, clinics, and chronic-care facilities, household members, visiting nurses, and volunteer workers. If an outbreak is caused by a variant strain of influenza that might not be controlled by the vaccine, chemoprophylaxis should be considered for all such persons, regardless of their vaccination status.

**Persons Who Have Immune Deficiencies.** Chemoprophylaxis can be considered for persons at high risk who are expected to have an inadequate antibody response to influenza vaccine. This category includes persons infected with HIV,



chiefly those with advanced HIV disease. No published data are available concerning possible efficacy of chemoprophylaxis among persons with HIV infection or interactions with other drugs used to manage HIV infection. Such patients should be monitored closely if chemoprophylaxis is administered.

**Other Persons.** Chemoprophylaxis throughout the influenza season or during peak influenza activity might be appropriate for persons at high risk who should not be vaccinated. Chemoprophylaxis can also be offered to persons who wish to avoid influenza illness. Health-care providers and patients should make this decision on an individual basis.

### Control of Influenza Outbreaks in Institutions

Using antiviral drugs for treatment and prophylaxis of influenza is a key component of influenza outbreak control in institutions. In addition to antiviral medications, other outbreak-control measures include instituting droplet precautions and establishing cohorts of patients with confirmed or suspected influenza, re-offering influenza vaccinations to unvaccinated staff and patients, restricting staff movement between wards or buildings, and restricting contact between ill staff or visitors and patients (270–272) (for additional information regarding outbreak control in specific settings, refer to additional references in Additional Information Regarding Influenza Infection Control Among Specific Populations).

The majority of published reports concerning use of antiviral agents to control influenza outbreaks in institutions are based on studies of influenza A outbreaks among nursing home populations where amantadine or rimantadine were used (222,250,257–259,269). Less information is available concerning use of neuraminidase inhibitors in influenza A or B institutional outbreaks (253,254,266,267,273). When confirmed or suspected outbreaks of influenza occur in institutions that house persons at high risk, chemoprophylaxis should be started as early as possible to reduce the spread of the virus. In these situations, having preapproved orders from physicians or plans to obtain orders for antiviral medications on short notice can substantially expedite administration of antiviral medications.

When outbreaks occur in institutions, chemoprophylaxis should be administered to all residents, regardless of whether they received influenza vaccinations during the previous fall, and should continue for a minimum of 2 weeks. If surveillance indicates that new cases continue to occur, chemoprophylaxis should be continued until approximately 1 week after the end of the outbreak. The dosage for each resident should be determined individually. Chemoprophylaxis also can be offered to unvaccinated staff who provide care to persons at

high risk. Prophylaxis should be considered for all employees, regardless of their vaccination status, if the outbreak is caused by a variant strain of influenza that is not well-matched by the vaccine.

In addition to nursing homes, chemoprophylaxis also can be considered for controlling influenza outbreaks in other closed or semiclosed settings (e.g., dormitories or other settings where persons live in close proximity). For example, chemoprophylaxis with rimantadine has been used successfully to control an influenza A outbreak aboard a large cruise ship (151).

To limit the potential transmission of drug-resistant virus during outbreaks in institutions, whether in chronic or acute-care settings or other closed settings, measures should be taken to reduce contact as much as possible between persons taking antiviral drugs for treatment and other persons, including those taking chemoprophylaxis (see Antiviral Drug-Resistant Strains of Influenza).

### Dosage

Dosage recommendations vary by age group and medical conditions (Table 4).

#### Children

**Amantadine.** Use of amantadine among children aged <1 year has not been adequately evaluated. The FDA-approved dosage for children aged 1–9 years for treatment and prophylaxis is 4.4–8.8 mg/kg/day, not to exceed 150 mg/day. Although further studies are needed to determine the optimal dosage for children aged 1–9 years, physicians should consider prescribing only 5 mg/kg/day (not to exceed 150 mg/day) to reduce the risk for toxicity. The approved dosage for children aged ≥10 years is 200 mg/day (100 mg twice a day); however, for children weighing <40 kg, prescribing 5 mg/kg/day, regardless of age, is advisable (252).

**Rimantadine.** Rimantadine is approved for prophylaxis among children aged ≥1 years and for treatment and prophylaxis among adults. Although rimantadine is approved only for prophylaxis of infection among children, certain specialists in the management of influenza consider it appropriate for treatment among children (217). Use of rimantadine among children aged <1 year has not been adequately evaluated. Rimantadine should be administered in 1 or 2 divided doses at a dosage of 5 mg/kg/day, not to exceed 150 mg/day for children aged 1–9 years. The approved dosage for children aged ≥10 years is 200 mg/day (100 mg twice a day); however, for children weighing <40 kg, prescribing 5 mg/kg/day, regardless of age, is recommended (274).

TABLE 4. Recommended daily dosage of influenza antiviral medications for treatment and prophylaxis

Antiviral agent	Age group (yrs)				
	1–6	7–9	10–12	13–64	≥65
<b>Amantadine*</b>					
Treatment, influenza A	5 mg/kg/day up to 150 mg in 2 divided doses <sup>†</sup>	5 mg/kg/day up to 150 mg in 2 divided doses <sup>†</sup>	100 mg twice daily <sup>§</sup>	100 mg twice daily <sup>§</sup>	≤100 mg/day
Prophylaxis, influenza A	5 mg/kg/day up to 150 mg in 2 divided doses <sup>†</sup>	5 mg/kg/day up to 150 mg in 2 divided doses <sup>†</sup>	100 mg twice daily <sup>§</sup>	100 mg twice daily <sup>§</sup>	≤100 mg/day
<b>Rimantadine<sup>¶</sup></b>					
Treatment, <sup>**</sup> influenza A	NA <sup>††</sup>	NA	NA	100 mg twice daily <sup>§§</sup>	100 mg/day
Prophylaxis, influenza A	5 mg/kg/day up to 150 mg in 2 divided doses <sup>†</sup>	5 mg/kg/day up to 150 mg in 2 divided doses <sup>†</sup>	100 mg twice daily <sup>§</sup>	100 mg twice daily <sup>§</sup>	100 mg/day <sup>¶¶</sup>
<b>Zanamivir<sup>***</sup> †††</b>					
Treatment, influenza A and B	NA	10 mg twice daily	10 mg twice daily	10 mg twice daily	10 mg twice daily
<b>Oseltamivir<sup>§§§</sup></b>					
Treatment, influenza A and B	Dose varies by child's weight <sup>¶¶¶</sup>	Dose varies by child's weight <sup>¶¶¶</sup>	Dose varies by child's weight <sup>¶¶¶</sup>	75 mg twice daily	75 mg twice daily
Prophylaxis, influenza A and B	NA	NA	NA	75 mg/day	75 mg/day

**NOTE:** Amantadine manufacturers include Endo Pharmaceuticals (Symmetrel<sup>®</sup> — tablet and syrup); Geneva Pharms Tech and Rosemont (Amantadine HCL — capsule); USL Pharma (Amantadine HCL — capsule and tablet); and Alpharma, Copley Pharmaceutical, HiTech Pharma, Mikart, Morton Grove, Carolina Medical, and Pharmaceutical Associates (Amantadine HCL — syrup). Rimantadine is manufactured by Forest Laboratories (Flumadine<sup>®</sup> — tablet and syrup) and Corepharma, Impax Labs (Rimantadine HCL — tablet), and Amide Pharmaceuticals (Rimantadine ACL — tablet). Zanamivir is manufactured by GlaxoSmithKline (Relenza<sup>®</sup> — inhaled powder). Oseltamivir is manufactured by Hoffman-LaRoche, Inc. (Tamiflu<sup>®</sup> — tablet). This information is based on data published by the Food and Drug Administration (FDA), which is available at <http://www.fda.gov>.

\* The drug package insert should be consulted for dosage recommendations for administering amantadine to persons with creatinine clearance ≤50 mL/min/1.73m<sup>2</sup>.

<sup>†</sup> 5 mg/kg of amantadine or rimantadine syrup = 1 tsp/22 lbs.

<sup>§</sup> Children aged ≥10 years who weigh <40 kg should be administered amantadine or rimantadine at a dosage of 5 mg/kg/day.

<sup>¶</sup> A reduction in dosage to 100 mg/day of rimantadine is recommended for persons who have severe hepatic dysfunction or those with creatinine clearance ≤10 mL/min. Other persons with less severe hepatic or renal dysfunction taking 100 mg/day of rimantadine should be observed closely, and the dosage should be reduced or the drug discontinued, if necessary.

<sup>\*\*</sup> Only approved by FDA for treatment among adults.

<sup>††</sup> Not applicable.

<sup>§§</sup> Rimantadine is approved by FDA for treatment among adults. However, certain specialists in the management of influenza consider rimantadine appropriate for treatment among children (see American Academy of Pediatrics. 2000 red book: report of the Committee on Infectious Diseases. 25<sup>th</sup> ed. Elk Grove Village, IL: American Academy of Pediatrics, 2000).

<sup>¶¶</sup> Older nursing-home residents should be administered only 100 mg/day of rimantadine. A reduction in dosage to 100 mg/day should be considered for all persons aged ≥65 years, if they experience possible side effects when taking 200 mg/day.

<sup>\*\*\*</sup> Zanamivir is administered through inhalation by using a plastic device included in the medication package. Patients will benefit from instruction and demonstration of correct use of the device.

<sup>†††</sup> Zanamivir is not approved for prophylaxis.

<sup>§§§</sup> A reduction in the dose of oseltamivir is recommended for persons with creatinine clearance <30 mL/min.

<sup>¶¶¶</sup> The dose 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. And, for children who weigh >40 kg, the dose is 75 mg twice a day.

**Zanamivir.** Zanamivir is approved for treatment among children aged  $\geq 7$  years. The recommended dosage of zanamivir for treatment of influenza is two inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) twice daily (approximately 12 hours apart) (233).

**Oseltamivir.** Oseltamivir is approved for treatment among persons aged  $\geq 1$  year and for chemoprophylaxis among persons age  $\geq 13$  years. Recommended treatment dosages for children vary by the weight of the child: the dosage recommendation for children who weigh  $\leq 15$  kg is 30 mg twice a day; for children weighing  $>15$ – $23$  kg, the dosage is 45 mg twice a day; for those weighing  $>23$ – $40$  kg, the dosage is 60 mg twice a day; and for children weighing  $>40$  kg, the dosage is 75 mg twice a day. The treatment dosage for persons aged  $\geq 13$  years is 75 mg twice daily. For children aged  $\geq 13$  years, the recommended dose for prophylaxis is 75 mg once a day (234).

### Persons Aged $\geq 65$ Years

**Amantadine.** The daily dosage of amantadine for persons aged  $\geq 65$  years should not exceed 100 mg for prophylaxis or treatment, because renal function declines with increasing age. For certain older persons, the dose should be further reduced.

**Rimantadine.** Among older persons, the incidence and severity of central nervous system (CNS) side effects are substantially lower among those taking rimantadine at a dosage of 100 mg/day than among those taking amantadine at dosages adjusted for estimated renal clearance (275). However, chronically ill older persons have had a higher incidence of CNS and gastrointestinal symptoms and serum concentrations 2–4 times higher than among healthy, younger persons when rimantadine has been administered at a dosage of 200 mg/day (222).

For prophylaxis among persons aged  $\geq 65$  years, the recommended dosage is 100 mg/day. For treatment of older persons in the community, a reduction in dosage to 100 mg/day should be considered if they experience side effects when taking a dosage of 200 mg/day. For treatment of older nursing home residents, the dosage of rimantadine should be reduced to 100 mg/day (274).

**Zanamivir and Oseltamivir.** No reduction in dosage is recommended on the basis of age alone.

### Persons with Impaired Renal Function

**Amantadine.** A reduction in dosage is recommended for patients with creatinine clearance  $\leq 50$  mL/min/1.73m<sup>2</sup>. Guidelines for amantadine dosage on the basis of creatinine clearance are located in the package insert. Because recommended dosages on the basis of creatinine clearance might

provide only an approximation of the optimal dose for a given patient, such persons should be observed carefully for adverse reactions. If necessary, further reduction in the dose or discontinuation of the drug might be indicated because of side effects. Hemodialysis contributes minimally to amantadine clearance (276,277).

**Rimantadine.** A reduction in dosage to 100 mg/day is recommended for persons with creatinine clearance  $<10$  mL/min. Because of the potential for accumulation of rimantadine and its metabolites, patients with any degree of renal insufficiency, including older persons, should be monitored for adverse effects, and either the dosage should be reduced or the drug should be discontinued, if necessary. Hemodialysis contributes minimally to drug clearance (278).

**Zanamivir.** Limited data are available regarding the safety and efficacy of zanamivir for patients with impaired renal function. Among patients with renal failure who were administered a single intravenous dose of zanamivir, decreases in renal clearance, increases in half-life, and increased systemic exposure to zanamivir were observed (233,279). However, a limited number of healthy volunteers who were administered high doses of intravenous zanamivir tolerated systemic levels of zanamivir that were substantially higher than those resulting from administration of zanamivir by oral inhalation at the recommended dose (280,281). On the basis of these considerations, the manufacturer recommends no dose adjustment for inhaled zanamivir for a 5-day course of treatment for patients with either mild to moderate or severe impairment in renal function (233).

**Oseltamivir.** Serum concentrations of oseltamivir carboxylate (GS4071), the active metabolite of oseltamivir, increase with declining renal function (234,238). For patients with creatinine clearance of 10–30 mL/min (234), a reduction of the treatment dosage of oseltamivir to 75 mg once daily and in the prophylaxis dosage to 75 mg every other day is recommended. No treatment or prophylaxis dosing recommendations are available for patients undergoing routine renal dialysis treatment.

### Persons with Liver Disease

**Amantadine.** No increase in adverse reactions to amantadine has been observed among persons with liver disease. Rare instances of reversible elevation of liver enzymes among patients receiving amantadine have been reported, although a specific relation between the drug and such changes has not been established (282).

**Rimantadine.** A reduction in dosage to 100 mg/day is recommended for persons with severe hepatic dysfunction.

**Zanamivir and Oseltamivir.** Neither of these medications has been studied among persons with hepatic dysfunction.

### Persons with Seizure Disorders

**Amantadine.** An increased incidence of seizures has been reported among patients with a history of seizure disorders who have received amantadine (283). Patients with seizure disorders should be observed closely for possible increased seizure activity when taking amantadine.

**Rimantadine.** Seizures (or seizure-like activity) have been reported among persons with a history of seizures who were not receiving anticonvulsant medication while taking rimantadine (284). The extent to which rimantadine might increase the incidence of seizures among persons with seizure disorders has not been adequately evaluated.

**Zanamivir and Oseltamivir.** Seizure events have been reported during postmarketing use of zanamivir and oseltamivir, although no epidemiologic studies have reported any increased risk for seizures with either zanamivir or oseltamivir use.

### Route

Amantadine, rimantadine, and oseltamivir are administered orally. Amantadine and rimantadine are available in tablet or syrup form, and oseltamivir is available in capsule or oral suspension form (209,210). Zanamivir is available as a dry powder that is self-administered via oral inhalation by using a plastic device included in the package with the medication. Patients will benefit from instruction and demonstration of correct use of this device (233).

## Pharmacokinetics

### Amantadine

Approximately 90% of amantadine is excreted unchanged in the urine by glomerular filtration and tubular secretion (257,285–288). Thus, renal clearance of amantadine is reduced substantially among persons with renal insufficiency, and dosages might need to be decreased (see Dosage) (Table 4).

### Rimantadine

Approximately 75% of rimantadine is metabolized by the liver (251). The safety and pharmacokinetics of rimantadine among persons with liver disease have been evaluated only after single-dose administration (251,289). In a study of persons with chronic liver disease (the majority with stabilized cirrhosis), no alterations in liver function were observed after

a single dose. However, for persons with severe liver dysfunction, the apparent clearance of rimantadine was 50% lower than that reported for persons without liver disease (274).

Rimantadine and its metabolites are excreted by the kidneys. The safety and pharmacokinetics of rimantadine among patients with renal insufficiency have been evaluated only after single-dose administration (251,278). Further studies are needed to determine multiple-dose pharmacokinetics and the most appropriate dosages for patients with renal insufficiency. In a single-dose study of patients with anuric renal failure, the apparent clearance of rimantadine was approximately 40% lower, and the elimination half-life was approximately 1.6-fold greater than that among healthy persons of the same age (278). Hemodialysis did not contribute to drug clearance. In studies of persons with less severe renal disease, drug clearance was also reduced, and plasma concentrations were higher than those among control patients without renal disease who were the same weight, age, and sex (274,290).

### Zanamivir

In studies of healthy volunteers, approximately 7%–21% of the orally inhaled zanamivir dose reached the lungs, and 70%–87% was deposited in the oropharynx (233,291). Approximately 4%–17% of the total amount of orally inhaled zanamivir is systemically absorbed. Systemically absorbed zanamivir has a half-life of 2.5–5.1 hours and is excreted unchanged in the urine. Unabsorbed drug is excreted in the feces (233,281).

### Oseltamivir

Approximately 80% of orally administered oseltamivir is absorbed systemically (238). Absorbed oseltamivir is metabolized to oseltamivir carboxylate, the active neuraminidase inhibitor, primarily by hepatic esterases. Oseltamivir carboxylate has a half-life of 6–10 hours and is excreted in the urine by glomerular filtration and tubular secretion via the anionic pathway (234,292). Unmetabolized oseltamivir also is excreted in the urine by glomerular filtration and tubular secretion (292).

## Side Effects and Adverse Reactions

When considering use of influenza antiviral medications (i.e., choice of antiviral drug, dosage, and duration of therapy), clinicians must consider the patient's age, weight, and renal function (Table 4); presence of other medical conditions; indications for use (i.e., prophylaxis or therapy); and the potential for interaction with other medications.



## Amantadine and Rimantadine

Both amantadine and rimantadine can cause CNS and gastrointestinal side effects when administered to young, healthy adults at equivalent dosages of 200 mg/day. However, incidence of CNS side effects (e.g., nervousness, anxiety, insomnia, difficulty concentrating, and lightheadedness) is higher among persons taking amantadine than among those taking rimantadine (293). In a 6-week study of prophylaxis among healthy adults, approximately 6% of participants taking rimantadine at a dosage of 200 mg/day experienced  $\geq 1$  CNS symptom, compared with approximately 13% of those taking the same dosage of amantadine and 4% of those taking placebo (293). A study of older persons also demonstrated fewer CNS side effects associated with rimantadine compared with amantadine (275). Gastrointestinal side effects (e.g., nausea and anorexia) occur in approximately 1%–3% of persons taking either drug, compared with 1% of persons receiving the placebo (293).

Side effects associated with amantadine and rimantadine are usually mild and cease soon after discontinuing the drug. Side effects can diminish or disappear after the first week, despite continued drug ingestion. However, serious side effects have been observed (e.g., marked behavioral changes, delirium, hallucinations, agitation, and seizures) (276,283). These more severe side effects have been associated with high plasma drug concentrations and have been observed most often among persons who have renal insufficiency, seizure disorders, or certain psychiatric disorders and among older persons who have been taking amantadine as prophylaxis at a dosage of 200 mg/day (257). Clinical observations and studies have indicated that lowering the dosage of amantadine among these persons reduces the incidence and severity of such side effects (Table 4). In acute overdosage of amantadine, CNS, renal, respiratory, and cardiac toxicity, including arrhythmias, have been reported (276). Because rimantadine has been marketed for a shorter period than amantadine, its safety among certain patient populations (e.g., chronically ill and older persons) has been evaluated less frequently. Because amantadine has anticholinergic effects and might cause mydriasis, it should not be used in patients with untreated angle closure glaucoma (276).

## Zanamivir

In a study of zanamivir treatment of influenza-like illness among persons with asthma or chronic obstructive pulmonary disease where study medication was administered after use of a B<sub>2</sub>-agonist, 13% of patients receiving zanamivir and 14% of patients who received placebo (inhaled powdered lactose vehicle) experienced a >20% decline in forced expiratory

volume in 1 second (FEV<sub>1</sub>) after treatment (233,235). However, in a phase-I study of persons with mild or moderate asthma who did not have influenza-like illness, 1 of 13 patients experienced bronchospasm after administration of zanamivir (233). In addition, during postmarketing surveillance, cases of respiratory function deterioration after inhalation of zanamivir have been reported. Certain patients had underlying airways disease (e.g., asthma or chronic obstructive pulmonary disease). Because of the risk for serious adverse events and because the efficacy has not been demonstrated among this population, zanamivir is not recommended for treatment for patients with underlying airway disease (233). If physicians decide to prescribe zanamivir to patients with underlying chronic respiratory disease after carefully considering potential risks and benefits, the drug should be used with caution under conditions of appropriate monitoring and supportive care, including the availability of short-acting bronchodilators (249). Patients with asthma or chronic obstructive pulmonary disease who use zanamivir are advised to 1) have a fast-acting inhaled bronchodilator available when inhaling zanamivir and 2) stop using zanamivir and contact their physician if they experience difficulty breathing (233). No definitive evidence is available regarding the safety or efficacy of zanamivir for persons with underlying respiratory or cardiac disease or for persons with complications of acute influenza (249). Allergic reactions, including oropharyngeal or facial edema, have also been reported during postmarketing surveillance (233,253).

In clinical treatment studies of persons with uncomplicated influenza, the frequencies of adverse events were similar for persons receiving inhaled zanamivir and those receiving placebo (i.e., inhaled lactose vehicle alone) (223–228,253). The most common adverse events reported by both groups were diarrhea; nausea; sinusitis; nasal signs and symptoms; bronchitis; cough; headache; dizziness; and ear, nose, and throat infections. Each of these symptoms was reported by <5% of persons in the clinical treatment studies combined (233).

## Oseltamivir

Nausea and vomiting were reported more frequently among adults receiving oseltamivir for treatment (nausea without vomiting, approximately 10%; vomiting, approximately 9%) than among persons receiving placebo (nausea without vomiting, approximately 6%; vomiting, approximately 3%) (229,230,234,294). Among children treated with oseltamivir, 14.3% had vomiting, compared with 8.5% of placebo recipients. Overall, 1% discontinued the drug secondary to this side effect (232), whereas a limited number of adults who were

enrolled in clinical treatment trials of oseltamivir discontinued treatment because of these symptoms (234). Similar types and rates of adverse events were reported in studies of oseltamivir prophylaxis (234). Nausea and vomiting might be less severe if oseltamivir is taken with food (234,294).

## Use During Pregnancy

No clinical studies have been conducted regarding the safety or efficacy of amantadine, rimantadine, zanamivir, or oseltamivir for pregnant women; only two cases of amantadine use for severe influenza illness during the third trimester have been reported (124,125). However, both amantadine and rimantadine have been demonstrated in animal studies to be teratogenic and embryotoxic when administered at substantially high doses (274,276). Because of the unknown effects of influenza antiviral drugs on pregnant women and their fetuses, these four drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus (see manufacturers' package inserts) (233,234,274,276).

## Drug Interactions

Careful observation is advised when amantadine is administered concurrently with drugs that affect CNS, including CNS stimulants. Concomitant administration of antihistamines or anticholinergic drugs can increase the incidence of adverse CNS reactions (222). No clinically substantial interactions between rimantadine and other drugs have been identified.

Clinical data are limited regarding drug interactions with zanamivir. However, no known drug interactions have been reported, and no clinically critical drug interactions have been predicted on the basis of *in vitro* data and data from studies using rats (233,295).

Limited clinical data are available regarding drug interactions with oseltamivir. Because oseltamivir and oseltamivir carboxylate are excreted in the urine by glomerular filtration and tubular secretion via the anionic pathway, a potential exists for interaction with other agents excreted by this pathway. For example, coadministration of oseltamivir and probenecid resulted in reduced clearance of oseltamivir carboxylate by approximately 50% and a corresponding approximate twofold increase in the plasma levels of oseltamivir carboxylate (234,292).

No published data are available concerning the safety or efficacy of using combinations of any of these four influenza antiviral drugs. For more detailed information concerning potential drug interactions for any of these influenza antiviral drugs, package inserts should be consulted.

## Antiviral Drug-Resistant Strains of Influenza

Amantadine-resistant viruses are cross-resistant to rimantadine and vice versa (296). Drug-resistant viruses can appear in approximately one third of patients when either amantadine or rimantadine is used for therapy (256,297,298). During the course of amantadine or rimantadine therapy, resistant influenza strains can replace sensitive strains within 2–3 days of starting therapy (297,299). Resistant viruses have been isolated from persons who live at home or in an institution where other residents are taking or have recently taken amantadine or rimantadine as therapy (300,301); however, the frequency with which resistant viruses are transmitted and their effect on efforts to control influenza are unknown. Amantadine- and rimantadine-resistant viruses are not more virulent or transmissible than sensitive viruses (302). The screening of epidemic strains of influenza A has rarely detected amantadine- and rimantadine-resistant viruses (297,303,304).

Persons who have influenza A infection and who are treated with either amantadine or rimantadine can shed sensitive viruses early in the course of treatment and later shed drug-resistant viruses, including after 5–7 days of therapy (256). Such persons can benefit from therapy even when resistant viruses emerge.

Resistance to zanamivir and oseltamivir can be induced in influenza A and B viruses *in vitro* (305–312), but induction of resistance requires multiple passages in cell culture. By contrast, resistance to amantadine and rimantadine *in vitro* can be induced with fewer passages in cell culture (313,314). Development of viral resistance to zanamivir and oseltamivir during treatment has been identified but does not appear to be frequent (234,315–318). In clinical treatment studies using oseltamivir, 1.3% of posttreatment isolates from patients aged  $\geq 13$  years and 8.6% among patients aged 1–12 years had decreased susceptibility to oseltamivir (234). No isolates with reduced susceptibility to zanamivir have been reported from clinical trials, although the number of posttreatment isolates tested is limited (319) and the risk for emergence of zanamivir-resistant isolates cannot be quantified (233). Only one clinical isolate with reduced susceptibility to zanamivir, obtained from an immunocompromised child on prolonged therapy, has been reported (316). Available diagnostic tests are not optimal for detecting clinical resistance to the neuraminidase inhibitor antiviral drugs, and additional tests are being developed (319,320). Postmarketing surveillance for neuraminidase inhibitor-resistant influenza viruses is being conducted (321).

## Sources of Information Regarding Influenza and Its Surveillance

Information regarding influenza surveillance, prevention, detection, and control is available on the CDC/National Center for Infectious Diseases website at <http://www.cdc.gov/ncidod/diseases/flu/weekly.htm>. Surveillance information is available through the CDC Voice Information System (influenza update) at 888-232-3228 or CDC Fax Information Service at 888-232-3299. During October–May, surveillance information is updated at least every other week. In addition, periodic updates regarding influenza are published in the *MMWR Weekly*. Additional information regarding influenza vaccine can be obtained at the CDC/National Immunization Program website at <http://www.cdc.gov/nip/flu> or by calling their hotline at 800-232-2522 (English) or 800-232-0233 (Spanish). State and local health departments should be consulted concerning availability of influenza vaccine, access to vaccination programs, information related to state or local influenza activity, and for reporting influenza outbreaks and receiving advice concerning outbreak control.

## Additional Information Regarding Influenza Infection Control Among Specific Populations

Each year, ACIP provides general, annually updated information regarding control and prevention of influenza. Other reports related to controlling and preventing influenza among specific populations (e.g., immunocompromised persons, health-care personnel, hospitals, and travelers) are also available in the following publications:

- CDC. Recommended adult immunization schedule — United States, 2002–03 [Notice to readers]. *MMWR* 2002;51:904–8.
- Garner JS, Hospital Infection Control Practices Advisory Committee. Guideline for isolation precautions in hospitals. *Infect Control Hosp Epidemiol* 1996;17:53–80.
- Tablan OC, Anderson LJ, Arden NH, et al., Hospital Infection Control Practices Advisory Committee. Guideline for prevention of nosocomial pneumonia. *Infect Control Hosp Epidemiol* 1994;15:587–627.
- Bolyard EA, Tablan OC, Williams WW, et al., Hospital Infection Control Practices Advisory Committee. Guideline for infection control in healthcare personnel. *Am J Infect Control* 1998;26:289–354.
- Bradley SF, The Long-Term–Care Committee of the Society for Healthcare Epidemiology of America. Prevention of influenza in long-term care facilities. *Infect Control Hosp Epidemiol* 1999;20:629–37.
- Sneller V-P, Izurieta H, Bridges C, et al. Prevention and control of vaccine-preventable diseases in long-term care facilities. *Journal of the American Medical Directors Association* 2000;1(Suppl):S2–37.
- American Academy of Pediatrics. 2000 red book: report of the Committee on Infectious Diseases. 25<sup>th</sup> ed. Elk Grove Village, IL: American Academy of Pediatrics, 2000.
- CDC. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Practitioners (AAFP). *MMWR* 2002;51 (No. RR-2):1–35.
- Bodnar UR, Maloney SA, Fielding KL, et al. Preliminary guidelines for the prevention and control of influenza-like illness among passengers and crew members on cruise ships. Atlanta, GA: US Department of Health and Human Services, CDC, National Center for Infectious Diseases, 1999.
- CDC. General recommendations for preventing influenza A infection among travelers. Atlanta, GA: US Department of Health and Human Services, CDC, 2001. Available at <http://www.cdc.gov/travel/feb99.htm>.
- US Public Health Service (USPHS) and Infectious Diseases Society of America (IDSA). USPHS/IDSA Prevention of Opportunistic Infections Working Group. 2001 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. Final November 28, 2001;1–65. Available at <http://www.aidsinfo.nih.gov>.
- CDC. Detection & control of influenza outbreaks in acute care facilities. Atlanta, GA: US Department of Health and Human Services, CDC, National Center for Infectious Diseases, 2001. Available at <http://www.cdc.gov/ncidod/hip/INFECT/FluBook2001.pdf>.

## References

1. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA* 2003;289:179–86.
2. Monto AS, Kioumeh F. Tecumseh study of respiratory illness. IX. Occurrence of influenza in the community, 1966–1971. *Am J Epidemiol* 1975;102:553–63.
3. Glezen WP, Couch RB. Interpandemic influenza in the Houston area, 1974–76. *N Engl J Med* 1978;298:587–92.
4. Glezen WP, Greenberg SB, Atmar RL, Piedra PA, Couch RB. Impact of respiratory virus infections on persons with chronic underlying conditions. *JAMA* 2000;283:499–505.
5. Barker WH. Excess pneumonia and influenza associated hospitalization during influenza epidemics in the United States, 1970–78. *Am J Public Health* 1986;76:761–5.
6. Barker WH, Mullooly JP. Impact of epidemic type A influenza in a defined adult population. *Am J Epidemiol* 1980;112(6):798–811.
7. Glezen WP. Serious morbidity and mortality associated with influenza epidemics. *Epidemiol Rev* 1982;4:25–44.
8. Office of Technology Assessment. Cost effectiveness of influenza vaccination. Washington, DC: US Congress, 1981.
9. Wilde JA, McMillan JA, Serwint J, Butta J, O’Riordan MA, Steinhoff MC. Effectiveness of influenza vaccine in health care professionals: a randomized trial. *JAMA* 1999;281:908–13.
10. Nichol KL, Lind A, Margolis KL, et al. Effectiveness of vaccination against influenza in healthy, working adults. *N Engl J Med* 1995;333:889–93.
11. Campbell DS, Rumley MH. Cost-effectiveness of the influenza vaccine in a healthy, working-age population. *J Occup Environ Med* 1997;39:408–14.
12. Bridges CB, Thompson WW, Meltzer MI, et al. Effectiveness and cost-benefit of influenza vaccination of healthy working adults: a randomized controlled trial. *JAMA* 2000;284:1655–63.
13. Patriarca PA, Weber JA, Parker RA, et al. Risk factors for outbreaks of influenza in nursing homes: a case-control study. *Am J Epidemiol* 1986;124:114–9.
14. Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA. Efficacy of influenza vaccine in elderly persons: a meta-analysis and review of the literature. *Ann Intern Med* 1995;123:518–27.
15. Mullooly JP, Bennett MD, Hornbrook MC, et al. Influenza vaccination programs for elderly persons: cost-effectiveness in a health maintenance organization. *Ann Intern Med* 1994;121:947–52.
16. Clements DA, Langdon L, Bland C, Walter E. Influenza A vaccine decreases the incidence of otitis media in 6- to 30-month-old children in day care. *Arch Pediatr Adolesc Med* 1995;149:1113–7.
17. Heikkinen T, Ruuskanen O, Waris M, Ziegler T, Arola M, Halonen P. Influenza vaccination in the prevention of acute otitis media in children. *Am J Dis Child* 1991;145:445–8.
18. Nordin J, Mullooly J, Poblete S, et al. Influenza vaccine effectiveness in preventing hospitalizations and deaths in persons 65 years or older in Minnesota, New York, and Oregon: data from 3 health plans. *J Infect Dis* 2001;184:665–70.
19. CDC. Vaccine-preventable diseases: improving vaccination coverage in children, adolescents, and adults: a report on recommendations of the Task Force on Community Preventive Services. *MMWR* 1999;48 (No. RR-8):1–15.
20. CDC. Use of standing orders programs to increase adult vaccination rates: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2000;49(No. RR-1):15–26.
21. Murphy BR, Webster RG. Orthomyxoviruses. In: Fields BN, Knipe DM, Howley PM, et al., eds. *Fields virology*. 3<sup>rd</sup> ed. Philadelphia, PA: Lippincott, 1996:1397–1445.
22. Clements ML, Betts RF, Tierney EL, Murphy BR. Serum and nasal wash antibodies associated with resistance to experimental challenge with influenza A wild-type virus. *J Clin Microbiol* 1986;24:157–60.
23. Couch RB, Kasel JA. Immunity to influenza in man. *Annu Rev Microbiol* 1983;37:529–49.
24. Cox NJ, Subbarao K. Influenza. *Lancet* 1999;354:1277–82.
25. Frank AL, Taber LH, Wells CR, Wells JM, Glezen WP, Paredes A. Patterns of shedding of myxoviruses and paramyxoviruses in children. *J Infect Dis* 1981;144:433–41.
26. Klimov AI, Rocha E, Hayden FG, Shult PA, Roumillat LF, Cox NJ. Prolonged shedding of amantadine-resistant influenza A viruses by immunodeficient patients: detection by polymerase chain reaction-restriction analysis. *J Infect Dis* 1995;172:1352–5.
27. Englund JA, Champlin RE, Wyde PR, et al. Common emergence of amantadine- and rimantadine-resistant influenza A viruses in symptomatic immunocompromised adults. *Clin Infect Dis* 1998;26:1418–24.
28. Boivin G, Goyette N, Bernatchez H. Prolonged excretion of amantadine-resistant influenza A virus quasi species after cessation of antiviral therapy in an immunocompromised patient. *Clin Infect Dis* 2002;34:23e–5e.
29. Nicholson KG. Clinical features of influenza. *Semin Respir Infect* 1992;7:26–37.
30. Ryan-Poirier K. Influenza virus infection in children. *Adv Pediatr Infect Dis* 1995;10:125–56.
31. Peltola V, Ziegler T, Ruuskanen O. Influenza A and B virus infections in children. *Clin Infect Dis* 2003;36:299–305.
32. Neuzil KM, Zhu Y, Griffin MR, et al. Burden of interpandemic influenza in children younger than 5 years: a 25-year prospective study. *J Infect Dis* 2002;185:147–52.
33. Boivin G, Hardy I, Tellier G, Maziade J. Predicting influenza infections during epidemics with use of a clinical case definition. *Clin Infect Dis* 2000;31:1166–9.
34. Monto AS, Gravenstein S, Elliott M, Colopy M, Schweinle J. Clinical signs and symptoms predicting influenza infection. *Arch Intern Med* 2000;160:3243–7.
35. Orenstein WA, Bernier RH, Hinman AR. Assessing vaccine efficacy in the field: further observations. *Epidemiol Rev* 1988;10:212–41.
36. Govaert TM, Dinant GJ, Aretz K, Knottnerus JA. Predictive value of influenza symptomatology in elderly people. *Fam Pract* 1998;15:16–22.
37. Walsh EE, Cox C, Falsey AR. Clinical features of influenza A virus infection in older hospitalized persons. *J Am Geriatr Soc* 2002;50:1498–1503.
38. Neuzil KM, O’Connor TZ, Gorse GJ, Nichol KL. Recognizing influenza in older patients with chronic obstructive pulmonary disease who have received influenza vaccine. *Clin Infect Dis* 2003;36:169–74.
39. Douglas RG Jr. Influenza in man. In: Kilbourne E, editor. *Influenza viruses and influenza*. New York, NY: Academic Press, Inc., 1975: 395–418.
40. Dagan R, Hall CB. Influenza A virus infection imitating bacterial sepsis in early infancy. *Pediatr Infect Dis* 1984;3:218–21.
41. Meibalane R, Sedmak GV, Sasidharan P, Garg P, Grausz JP. Outbreak of influenza in a neonatal intensive care unit. *J Pediatr* 1977;91:974–6.



42. Chiu SS, Tse CY, Lau YL, Peiris M. Influenza A infection is an important cause of febrile seizures. *Pediatrics* 2001;108:E63.
43. McCullers JA, Facchini S, Chesney PJ, Webster RG. Influenza B virus encephalitis. *Clin Infect Dis* 1999;28:898–900.
44. Morishima T, Togashi T, Yokota S, et al. Encephalitis and encephalopathy associated with an influenza epidemic in Japan. *Clin Infect Dis* 2002;35:512–7.
45. Simonsen L, Schonberger LB, Stroup DF, Arden N, Cox NJ. Impact of influenza on mortality in the USA. In: Brown LE, Hampson AW, Webster RG, eds. *Proceedings of the 3<sup>rd</sup> International Conference on Options for the Control of Influenza*, Cairns, Australia. Amsterdam: Elsevier Science, 1996:26–32.
46. Lui KJ, Kendal AP. Impact of influenza epidemics on mortality in the United States from October 1972 to May 1985. *Am J Public Health* 1987;77:712–6.
47. Noble GR. Epidemiological and clinical aspects of influenza. In: Beare AS, editor. *Basic and applied influenza research*. Boca Raton: CRC Press, 1982:11–50.
48. Eickhoff TC, Sherman IL, Serfling RE. Observations on excess mortality associated with epidemic influenza. *JAMA* 1961;176:776–82.
49. Barker WH, Mullooly JP. Pneumonia and influenza deaths during epidemics: implications for prevention. *Arch Intern Med* 1982;142:85–9.
50. Simonsen L, Clarke MJ, Schonberger LB, Arden NH, Cox NJ, Fukuda K. Pandemic versus epidemic influenza mortality: a pattern of changing age distribution. *J Infect Dis* 1998;178:53–60.
51. Glezen WP, Decker M, Perrotta DM. Survey of underlying conditions of persons hospitalized with acute respiratory disease during influenza epidemics in Houston, 1978–1981. *Am Rev Respir Dis* 1987;136:550–5.
52. Neuzil KM, Wright PF, Mitchel EF, Griffin MR. Burden of influenza illness in children with asthma and other chronic medical conditions. *J Pediatr* 2000;137:856–64.
53. Izurieta HS, Thompson WW, Kramarz P, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. *N Engl J Med* 2000;342:232–9.
54. Neuzil KM, Mellen BG, Wright PF, Mitchel EF, Griffin MR. Effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. *N Engl J Med* 2000;342:225–31.
55. Simonsen L, Fukuda K, Schonberger LB, Cox NJ. Impact of influenza epidemics on hospitalizations. *J Infect Dis* 2000;181:831–7.
56. National Center for Health Statistics. *Health, United States, 1998*. Hyattsville, MD: US Department of Health and Human Services, CDC, 1998. DHHS publication no. (PHS) 98-1232.
57. Simonsen L, Clarke MJ, Williamson GD, Stroup DF, Arden NH, Schonberger LB. Impact of influenza epidemics on mortality: introducing a severity index. *Am J Public Health* 1997;87:1944–50.
58. Kilbourne ED. *Influenza*. New York, NY: Plenum Medical Book Company, 1987.
59. CDC. Recommendations regarding the use of vaccines that contain thimerosal as a preservative. *MMWR* 1999;48:996–8.
60. Pichichero ME, Cernichiari E, Lopreiato J, Treanor J. Mercury concentrations and metabolism in infants receiving vaccines containing thiomersal: a descriptive study. *Lancet* 2002;360:1737–41.
61. Stratton K, Gable A, McCormick MC, eds. *Immunization safety review: thimerosal-containing vaccines and neurodevelopmental disorders*. Washington, DC: National Academy Press, 2001.
62. CDC. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Family Physicians (AAFP). *MMWR* 2002;51:1–35.
63. CDC. Summary of the joint statement on thimerosal in vaccines [Notice to readers]. *MMWR* 2000;49:622, 631.
64. La Montagne JR, Noble GR, Quinnan GV, et al. Summary of clinical trials of inactivated influenza vaccine—1978. *Rev Infect Dis* 1983;5:723–36.
65. Oxford JS, Schild GC, Potter CW, Jennings R. Specificity of the anti-haemagglutinin antibody response induced in man by inactivated influenza vaccines and by natural infection. *J Hyg (Lond)* 1979;82:51–61.
66. Neuzil KM, Dupont WD, Wright PF, Edwards KM. Efficacy of inactivated and cold-adapted vaccines against influenza A infection, 1985 to 1990: the pediatric experience. *Pediatr Infect Dis J* 2001;20:733–40.
67. Potter CW, Oxford JS. Determinants of immunity to influenza infection in man. *Br Med Bull* 1979;35:69–75.
68. Hirota Y, Kaji M, Ide S, et al. Antibody efficacy as a keen index to evaluate influenza vaccine effectiveness. *Vaccine* 1997;15:962–67.
69. Palache AM. Influenza vaccines: a reappraisal of their use. *Drugs* 1997;54:841–56.
70. Demicheli V, Jefferson T, Rivetti D, Deeks J. Prevention and early treatment of influenza in healthy adults. *Vaccine* 2000;18:957–1030.
71. Smith JW, Pollard R. Vaccination against influenza: a five-year study in the Post Office. *J Hyg (Lond)* 1979;83:157–70.
72. Gonzalez M, Pirez MC, Ward E, Dibarboure H, Garcia A, Picolet H. Safety and immunogenicity of a paediatric presentation of an influenza vaccine. *Arch Dis Child* 2000;83:488–91.
73. Wright PF, Cherry JD, Foy HM, et al. Antigenicity and reactogenicity of influenza A/USSR/77 virus vaccine in children—a multicentered evaluation of dosage and safety. *Rev Infect Dis* 1983;5(4):758–64.
74. Wright PF, Thompson J, Vaughn WK, Folland DS, Sell SH, Karzon DT. Trials of influenza A/New Jersey/76 virus vaccine in normal children: an overview of age-related antigenicity and reactogenicity. *J Infect Dis* 1977;136 (Suppl):S731–41.
75. Daubeney P, Taylor CJ, McGaw J, et al. Immunogenicity and tolerability of a trivalent influenza subunit vaccine (Influvac®) in high-risk children aged 6 months to 4 years. *Br J Clin Pract* 1997;51:87–90.
76. Groothuis JR, Lehr MV, Levin MJ. Safety and immunogenicity of a purified haemagglutinin antigen in very young high-risk children. *Vaccine* 1994;12:139–41.
77. Park CL, Frank AL, Sullivan M, Jindal P, Baxter BD. Influenza vaccination of children during acute asthma exacerbation and concurrent prednisone therapy. *Pediatrics* 1996;98:196–200.
78. Clover RD, Crawford S, Glezen WP, Taber LH, Matson CC, Couch RB. Comparison of heterotypic protection against influenza A/Taiwan/86 (H1N1) by attenuated and inactivated vaccines to A/Chile/83-like viruses. *J Infect Dis* 1991;163:300–4.
79. Sugaya N, Nerome K, Ishida M, Matsumoto M, Mitamura K, Nirasawa M. Efficacy of inactivated vaccine in preventing antigenically drifted influenza type A and well-matched type B. *JAMA* 1994;272:1122–6.
80. Hoberman A, Greenberg DP, Paradise JI, et al. Efficacy of inactivated influenza vaccine in preventing acute otitis media (AOM) in children [Abstract 752759]. Presented at the Pediatric Academic Societies' Annual Meeting, Baltimore, MD, 2002.

81. Blumberg EA, Albano C, Pruett T, et al. Immunogenicity of influenza virus vaccine in solid organ transplant recipients. *Clin Infect Dis* 1996;22:295–302.
82. Dorrell L, Hassan I, Marshall S, Chakraverty P, Ong E. Clinical and serological responses to an inactivated influenza vaccine in adults with HIV infection, diabetes, obstructive airways disease, elderly adults and healthy volunteers. *Int J STD AIDS* 1997;8:776–9.
83. McElhaney JE, Beattie BL, Devine R, Grynock R, Toth EL, Bleackley RC. Age-related decline in interleukin 2 production in response to influenza vaccine. *J Am Geriatr Soc* 1990;38:652–8.
84. Govaert TM, Thijs CT, Masurel N, Sprenger MJ, Dinant GJ, Knottnerus JA. Efficacy of influenza vaccination in elderly individuals: a randomized double-blind placebo-controlled trial. *JAMA* 1994;272:1661–5.
85. Hak E, Nordin J, Wei F, et al. Influence of high-risk medical conditions on the effectiveness of influenza vaccination among elderly members of 3 large managed-care organizations. *Clin Infect Dis* 2002;35:370–7.
86. Nichol KL, Wuorenma J, von Sternberg T. Benefits of influenza vaccination for low-, intermediate-, and high-risk senior citizens. *Arch Intern Med* 1998;158:1769–76.
87. Patriarca PA, Weber JA, Parker RA, et al. Efficacy of influenza vaccine in nursing homes reduction in illness and complications during an Influenza A (H3N2) epidemic. *JAMA* 1985;253:1136–9.
88. Arden NH, Patriarca PA, Kendal AP. Experiences in the use and efficacy of inactivated influenza vaccine in nursing homes. *Options for the Control of Influenza* 1986;155–68.
89. Monto AS, Hornbuckle K, Ohmit SE. Influenza vaccine effectiveness among elderly nursing home residents: a cohort study. *Am J Epidemiol* 2001;154:155–60.
90. Riddiough MA, Sisk JE, Bell JC. Influenza vaccination. *JAMA* 1983;249:3189–95.
91. Mixeu MA, Vespa GNR, Forleo-Neto E, Toniolo-Neto J, Alves PM. Impact of influenza vaccination on civilian aircrew illness and absenteeism. *Aviat Space Environ Med* 2002;73:876–80.
92. Nichol KL. Cost-benefit analysis of a strategy to vaccinate healthy working adults against influenza. *Arch Intern Med* 2001;161:749–59.
93. Cohen GM, Nettleman MD. Economic impact of influenza vaccination in preschool children. *Pediatrics* 2000;106:973–6.
94. White T, Lavoie S, Nettleman MD. Potential cost savings attributable to influenza vaccination of school-aged children. *Pediatrics* 1999;103:73e.
95. Dayan GH, Nguyen VH, Debbag R, Gomez R, Wood SC. Cost-effectiveness of influenza vaccination in high-risk children in Argentina. *Vaccine* 2001;19:4204–13.
96. CDC. Influenza and pneumococcal vaccination coverage levels among persons aged  $\geq 65$  years—United States, 1973–1993. *MMWR* 1995;44:506–7, 513–5.
97. CDC. Early release of selected estimates based on data from the January–June 2002 NHIS. Hyattsville, MD: US Department of Health and Human Services, CDC, National Center for Health Statistics, 2002. Available at <http://www.cdc.gov/nchs/about/major/nhis/released200212.htm>.
98. US Department of Health and Human Services, PHS. Healthy people 2000: national health promotion and disease prevention objectives—full report, with commentary. Washington, DC: US Department of Health and Human Services, Public Health Service, 1991.
99. CDC. Implementation of the Medicare influenza vaccination benefit—United States, 1993. *MMWR* 1994;43:771–3.
100. Singleton JA, Greby SM, Wooten KG, Walker FJ, Strikas R. Influenza, pneumococcal, and tetanus toxoid vaccination of adults—United States, 1993–1997. *MMWR* 2000;49(No. SS-9):39–62.
101. US Department of Health and Human Services. Healthy people 2010 (conference ed., in 2 vols). Washington, DC: US Department of Health and Human Services, 2000.
102. CDC. Influenza and pneumococcal vaccination levels among persons aged  $>65$  years—United States, 2001. *MMWR* 2002;51:1019–24.
103. Buikema AR, Singleton JA, Sneller VP, Strikas RA. Influenza vaccination in nursing homes, United States, 1995 and 1997 [Abstract P2-49]. Presented at the Options for the Control of Influenza IV conference, Crete, Greece, September 23–28, 2000.
104. Zadeh MM, Buxton BC, Thompson WW, Arden NH, Fukuda K. Influenza outbreak detection and control measures in nursing homes in the United States. *J Am Geriatr Soc* 2000;48:1310–5.
105. Kramarz P, DeStefano F, Gargiullo PM, et al. Influenza vaccination in children with asthma in health maintenance organizations. Vaccine Safety Datalink Team. *Vaccine* 2000;18:2288–94.
106. Chung EK, Casey R, Pinto-Martin JA, Pawlowski NA, Bell LM. Routine and influenza vaccination rates in children with asthma. *Ann Allergy Asthma Immunol* 1998;80:318–22.
107. Gaglani M, Riggs M, Kamenicky C, Glezen WP. Computerized reminder strategy is effective for annual influenza immunization of children with asthma or reactive airway disease. *Pediatr Infect Dis J* 2001;20:1155–60.
108. Marshall BC, Henshaw C, Evans DA, Bleyl K, Alder S, Liou TG. Influenza vaccination coverage level at a cystic fibrosis center. *Pediatrics* 2002;109:E80.
109. Walker FJ, Singleton JA, Lu PJ, Strikas RA. Influenza vaccination of healthcare workers in the United States, 1989–97. *Infect Control Hosp Epidemiol* 2000;21:113.
110. Potter J, Stott DJ, Roberts MA, et al. Influenza vaccination of health care workers in long-term-care hospitals reduces the mortality of elderly patients. *J Infect Dis* 1997;175:1–6.
111. Carman WF, Elder AG, Wallace LA, et al. Effects of influenza vaccination of health-care workers on mortality of elderly people in long-term care: a randomised controlled trial. *Lancet* 2000;355:93–7.
112. Lu PJ, Singleton JA. Influenza vaccination of pregnant women: Behavioral Risk Factor Surveillance System (BRFSS), 1997–2001. Annual Behavioral Risk Factor Surveillance System Conference, St. Louis, MO, 2003.
113. Yeager DP, Toy EC, Baker B, III. Influenza vaccination in pregnancy. *Am J Perinatol* 1999;16:283–6.
114. Gonik B, Jones T, Contreras D, Fasano N, Roberts C. Obstetrician-gynecologist's role in vaccine-preventable diseases and immunization. *Obstet Gynecol* 2000;96:81–4.
115. Fukuda K, O'Mara D, Singleton JA. Drug Shortages, Part 4: how the delayed distribution of influenza vaccine created shortages in 2000 and 2001. *Pharm Therapeutics* 2002;27:235–42.
116. CDC. Assessing adult vaccination status at age 50 years [Notice to readers]. *MMWR* 1995;44:561–3.
117. Fedson DS. Adult immunization: summary of the National Vaccine Advisory Committee Report. *JAMA* 1994;272:1133–7.
118. Noble GR. Epidemiological and clinical aspects of influenza. In: Beare AS, editor. Basic and applied influenza research. Boca Raton: CRC Press, 1982:11–50.

119. Harris JW. Influenza occurring in pregnant women: a statistical study of thirteen hundred and fifty cases. *JAMA* 1919;72:978–80.
120. Widelock D, Csizmas L, Klein S. Influenza, pregnancy, and fetal outcome. *Am J Obstet Gynecol* 1963;78.
121. Freeman DW, Barno A. Deaths from Asian influenza associated with pregnancy. *Am J Obstet Gynecol* 1959;78:1172–5.
122. Shahab SZ, Glezen WP. Influenza virus. In: Gonik B, ed. *Viral diseases in pregnancy*. New York, NY: Springer-Verlag, 1994:215–23.
123. Schoenbaum SC, Weinstein L. Respiratory infection in pregnancy. *Clin Obstet Gynecol* 1979;22:293–300.
124. Kirshon B, Faro S, Zurawin RK, Samo TC, Carpenter RJ. Favorable outcome after treatment with amantadine and ribavirin in a pregnancy complicated by influenza pneumonia: a case report. *J Reprod Med* 1988;33:399–401.
125. Kort BA, Cefalo RC, Baker VV. Fatal influenza A pneumonia in pregnancy. *Am J Perinatol* 1986;3:179–82.
126. Irving WL, James DK, Stephenson T, et al. Influenza virus infection in the second and third trimesters of pregnancy: a clinical and seroepidemiological study. *British Journal of Obstetrics and Gynaecology* 2000;107:1282–9.
127. Neuzil KM, Reed GW, Mitchel EF, Simonsen L, Griffin MR. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. *Am J Epidemiol* 1998;148:1094–1102.
128. Anonymous. Immunization during pregnancy. *ACOG Technical Bulletin* 1999;160:1–11.
129. Heinonen OP, Shapiro S, Monson RR, Hartz SC, Rosenberg L, Slone D. Immunization during pregnancy against poliomyelitis and influenza in relation to childhood malignancy. *Int J Epidemiol* 1973;2:229–35.
130. Couch RB. Influenza, influenza virus vaccine, and human immunodeficiency virus infection. *Clin Infect Dis* 1999;28:548–51.
131. Tasker SA, O'Brien WA, Treanor JJ, et al. Effects of influenza vaccination in HIV-infected adults: a double-blind, placebo-controlled trial. *Vaccine* 1998;16:1039–42.
132. Neuzil KM, Reed GW, Mitchel EF, Griffin MR. Influenza-associated morbidity and mortality in young and middle-aged women. *JAMA* 1999;281:901–7.
133. Lin JC, Nichol KL. Excess mortality due to pneumonia or influenza during influenza seasons among persons with acquired immunodeficiency syndrome. *Arch Intern Med* 2001;161:441–6.
134. Safrin S, Rush JD, Mills J. Influenza in patients with human immunodeficiency virus infection. *Chest* 1990;98:33–7.
135. Radwan HM, Cheeseman SH, Lai KK, Ellison RT III. Influenza in human immunodeficiency virus-infected patients during the 1997–1998 influenza season. *Clin Infect Dis* 2000;31:604–6.
136. Fine AD, Bridges CB, De Guzman AM, et al. Influenza A among patients with human immunodeficiency virus: an outbreak of infection at a residential facility in New York City. *Clin Infect Dis* 2001;32:1784–91.
137. Chadwick EG, Chang G, Decker MD, Yogev R, Dimichele D, Edwards KM. Serologic response to standard inactivated influenza vaccine in human immunodeficiency virus-infected children. *Pediatr Infect Dis J* 1994;13:206–11.
138. Huang KL, Ruben FL, Rinaldo CR Jr., Kingsley L, Lyter DW, Ho M. Antibody responses after influenza and pneumococcal immunization in HIV-infected homosexual men. *JAMA* 1987;257:2047–50.
139. Staprans SI, Hamilton BL, Follansbee SE, et al. Activation of virus replication after vaccination of HIV-1-infected individuals. *J Exp Med* 1995;182:1727–37.
140. Kroon FP, van Dissel JT, de Jong JC, Zwinderman K, van Furth R. Antibody response after influenza vaccination in HIV-infected individuals: a consecutive 3-year study. *Vaccine* 2000;18:3040–9.
141. Miotti PG, Nelson KE, Dallabetta GA, Farzadegan H, Margolick J, Clements ML. Influence of HIV infection on antibody responses to a two-dose regimen of influenza vaccine. *JAMA* 1989;262:779–83.
142. Ho DD. HIV-1 viraemia and influenza [Letter]. *Lancet* 1992;339:1549.
143. O'Brien WA, Grovit-Ferbas K, Namazi A, et al. Human immunodeficiency virus—type 1 replication can be increased in peripheral blood of seropositive patients after influenza vaccination. *Blood* 1995;86:1082–9.
144. Glesby MJ, Hoover DR, Farzadegan H, Margolick JB, Saah AJ. Effect of influenza vaccination on human immunodeficiency virus type 1 load: a randomized, double-blind, placebo-controlled study. *J Infect Dis* 1996;174:1332–6.
145. Fowke KR, D'Amico R, Chernoff DN, et al. Immunologic and virologic evaluation after influenza vaccination of HIV-1-infected patients. *AIDS* 1997;11:1013–21.
146. Fuller JD, Craven DE, Steger KA, Cox N, Heeren TC, Chernoff D. Influenza vaccination of human immunodeficiency virus (HIV)-infected adults: impact on plasma levels of HIV type 1 RNA and determinants of antibody response. *Clin Infect Dis* 1999;28:541–7.
147. Amendola A, Boschini A, Colzani D, et al. Influenza vaccination of HIV-1-positive and HIV-1-negative former intravenous drug users. *J Med Virol* 2001;65:644–8.
148. Sullivan PS, Hanson DL, Dworkin MS, Jones JL, Ward JW. Effect of influenza vaccination on disease progression among HIV-infected persons. *Adult and Adolescent Spectrum of HIV Disease Investigators*. *AIDS* 2000;14:2781–5.
149. Gunthard HF, Wong JK, Spina CA, et al. Effect of influenza vaccination on viral replication and immune response in persons infected with human immunodeficiency virus receiving potent antiretroviral therapy. *J Infect Dis* 2000;181:522–31.
150. Miller JM, Tam TW, Maloney S, et al. Cruise ships: high-risk passengers and the global spread of new influenza viruses. *Clin Infect Dis* 2000;31:433–8.
151. Uyeki TM, Zane SB, Bodnar UR, et al. Large summertime Influenza A outbreak among tourists in Alaska and the Yukon Territory, 2003. *Clin Infect Dis* (In press).
152. Mullooly JP, Barker WH. Impact of type A influenza on children: a retrospective study. *Am J Public Health* 1982;72:1008–16.
153. Glezen WP, Decker M, Joseph SW, Mercready RG Jr. Acute respiratory disease associated with influenza epidemics in Houston, 1981–1983. *J Infect Dis* 1987;155:1119–26.
154. Cooney MK, Fox JP, Hall CE. Seattle Virus Watch. VI. Observations of infections with and illness due to parainfluenza, mumps and respiratory syncytial viruses and *Mycoplasma pneumoniae*. *Am J Epidemiol* 1975;101:532–51.
155. Glezen WP, Taber LH, Frank AL, Kasel JA. Risk of primary infection and reinfection with respiratory syncytial virus. *Am J Dis Child* 1986;140:543–6.
156. Glezen WP. Morbidity associated with the major respiratory viruses. *Pediatr Ann* 1990;19:535–6, 538, 540.

157. Reduction of the influenza burden in children. *Pediatrics* 2002;110:1246–52.
158. CDC. Expansion of eligibility for influenza vaccine through the Vaccines for Children Program [Notice to readers]. *MMWR* 2002;51:864, 875.
159. Gross PA, Russo C, Dran S, Cataruozolo P, Munk G, Lancey SC. Time to earliest peak serum antibody response to influenza vaccine in the elderly. *Clin Diagn Lab Immunol* 1997;4:491–2.
160. Brokstad KA, Cox RJ, Olofsson J, Jonsson R, Haaheim LR. Parenteral influenza vaccination induces a rapid systemic and local immune response. *J Infect Dis* 1995;171:198–203.
161. McElhaney JE, Gravenstein S, Upshaw CM, Hooton JW, Krause P, Drinka P. Immune response to influenza vaccination in institutionalized elderly: effect on different T-cell subsets. *Vaccine* 1998;16:403–9.
162. Gross PA, Weksler ME, Quinnan GV, Douglas RG, Gaerlan PF, Denning CR. Immunization of elderly people with two doses of influenza vaccine. *J Clin Microbiol* 1987;25:1763–5.
163. Feery BJ, Cheyne IM, Hampson AW, Atkinson MI. Antibody response to one and two doses of influenza virus subunit vaccine. *Med J Aust* 1976;1:186–9.
164. Levine M, Beattie BL, McLean DM. Comparison of one- and two-dose regimens of influenza vaccine for elderly men. *CMAJ* 1987;137:722–6.
165. Cate TR, Couch RB, Parker D, Baxter B. Reactogenicity, immunogenicity, and antibody persistence in adults given inactivated influenza virus vaccines—1978. *Rev Infect Dis* 1983;5:737–47.
166. Kunzel W, Glathe H, Engelmann H, Van Hoecke C. Kinetics of humoral antibody response to trivalent inactivated split influenza vaccine in subjects previously vaccinated or vaccinated for the first time. *Vaccine* 1996;14:1108–10.
167. Poland GA, Borrud A, Jacobson RM, et al. Determination of deltoid fat pad thickness: implications for needle length in adult immunization. *JAMA* 1997;277:1709–11.
168. Govaert TME, Dinant GJ, Aretz K, Masurel N, Sprenger MJW, Knottnerus JA. Adverse reactions to influenza vaccine in elderly people: randomised double blind placebo controlled trial. *BMJ* 1993;307:988–90.
169. Margolis KL, Nichol KL, Poland GA, Pluhar RE. Frequency of adverse reactions to influenza vaccine in the elderly: a randomized, placebo-controlled trial. *JAMA* 1990;264:1139–41.
170. Nichol KL, Margolis KL, Lind A, et al. Side effects associated with influenza vaccination in healthy working adults: a randomized, placebo-controlled trial. *Arch Intern Med* 1996;156:1546–50.
171. American Lung Association Asthma Clinical Research Centers. Safety of inactivated influenza vaccine in adults and children with asthma. *N Engl J Med* 2001;345:1529–36.
172. Piedra PA, Glezen WP, Mbawuike I, et al. Studies on reactogenicity and immunogenicity of attenuated bivalent cold recombinant influenza type A (CRA) and inactivated trivalent influenza virus (TI) vaccines in infants and young children. *Vaccine* 1993;11:718–24.
173. Scheifele DW, Bjornson G, Johnston J. Evaluation of adverse events after influenza vaccination in hospital personnel. *CMAJ* 1990;142:127–30.
174. Barry DW, Mayner RE, Hochstein HD, et al. Comparative trial of influenza vaccines. II. Adverse reactions in children and adults. *Am J Epidemiol* 1976;104:47–59.
175. France EK, Jackson L, Vaccine Safety Datalink Team, et al. Safety of the trivalent inactivated influenza vaccine among children: a population-based study [Abstract 76]. Presented at the National Immunization Conference, Chicago, IL, 2003.
176. Groothuis JR, Levin MJ, Rabalais GP, Meiklejohn G, Lauer BA. Immunization of high-risk infants younger than 18 months of age with split-product influenza vaccine. *Pediatrics* 1991;87:823–8.
177. Bierman CW, Shapiro GG, Pierson WE, Taylor JW, Foy HM, Fox JP. Safety of influenza vaccination in allergic children. *J Infect Dis* 1977;136(Suppl):S652–5.
178. James JM, Zeiger RS, Lester MR, et al. Safe administration of influenza vaccine to patients with egg allergy. *J Pediatr* 1998;133:624–8.
179. Murphy KR, Strunk RC. Safe administration of influenza vaccine in asthmatic children hypersensitive to egg proteins. *J Pediatr* 1985;106:931–3.
180. Zeiger RS. Current issues with influenza vaccination in egg allergy. *J Allergy Clin Immunol* 2002;110:834–40.
181. Aberer W. Vaccination despite thimerosal sensitivity. *Contact Dermatitis* 1991;24:6–10.
182. Kirkland LR. Ocular sensitivity to thimerosal: a problem with hepatitis B vaccine? *South Med J* 1990;83:497–9.
183. Schonberger LB, Bregman DJ, Sullivan-Bolyai JZ, et al. Guillain-Barré syndrome following vaccination in the National Influenza Immunization Program, United States, 1976–1977. *Am J Epidemiol* 1979;110:105–23.
184. Safranek TJ, Lawrence DN, Kurland LT, et al. Reassessment of the association between Guillain-Barré syndrome and receipt of swine influenza vaccine in 1976–1977: results of a two-state study. *Expert Neurology Group. Am J Epidemiol* 1991;133:940–51.
185. Ropper AH. Guillain-Barré Syndrome. *N Engl J Med* 1992;326:1130–6.
186. Hurwitz ES, Schonberger LB, Nelson DB, Holman RC. Guillain-Barré syndrome and the 1978–1979 influenza vaccine. *N Engl J Med* 1981;304:1557–61.
187. Kaplan JE, Katona P, Hurwitz ES, Schonberger LB. Guillain-Barré syndrome in the United States, 1979–1980 and 1980–1981: lack of an association with influenza vaccination. *JAMA* 1982;248:698–700.
188. Chen R, Kent J, Rhodes P, Simon P, Schonberger L. Investigation of a possible association between influenza vaccination and Guillain-Barré syndrome in the United States, 1990–1991 [Abstract 0404]. In: *Post Marketing Surveillance*, 1992.
189. Lasky T, Terracciano GJ, Magder L, et al. Guillain-Barré syndrome and the 1992–1993 and 1993–1994 influenza vaccines. *N Engl J Med* 1998;339:1797–1802.
190. Flewett TH, Houlst JG. Influenzal encephalopathy and postinfluenzal encephalitis. *Lancet* 1958;11–20.
191. Horner FA. Neurologic disorders after Asian influenza. *N Engl J Med* 1958;258:983–5.
192. Jacobs BC, Rothbarth PH, van der Meche FG, et al. Spectrum of antecedent infections in Guillain-Barré syndrome: a case-control study. *Neurology* 1998;51:1110–5.
193. Guarino M, Casmiro M, D'Alessandro R. *Campylobacter jejuni* infection and Guillain-Barré syndrome: a case-control study. Emilia-Romagna Study Group on Clinical and Epidemiological Problems in Neurology. *Neuroepidemiology* 1998;17:296–302.



194. Sheikh KA, Nachamkin I, Ho TW, et al. *Campylobacter jejuni* lipopolysaccharides in Guillain-Barré syndrome: molecular mimicry and host susceptibility. *Neurology* 1998;51:371–8.
195. Prevots DR, Sutter RW. Assessment of Guillain-Barré syndrome mortality and morbidity in the United States: implications for acute flaccid paralysis surveillance. *J Infect Dis* 1997;175(Suppl 1):S151–5.
196. Barohn RJ, Saperstein DS. Guillain-Barré syndrome and chronic inflammatory demyelinating polyneuropathy. *Semin Neurol* 1998;18:49–61.
197. CDC. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1997;46(No. RR-8):1–24.
198. Grilli G, Fuiano L, Biasio LR, et al. Simultaneous influenza and pneumococcal vaccination in elderly individuals. *Eur J Epidemiol* 1997;13:287–91.
199. Fletcher TJ, Tunnicliffe WS, Hammond K, Roberts K, Ayres JG. Simultaneous immunisation with influenza vaccine and pneumococcal polysaccharide vaccine in patients with chronic respiratory disease. *BMJ* 1997;314:1663–5.
200. Lawson F, Baker V, Au D, McElhaney JE. Standing orders for influenza vaccination increased vaccination rates in inpatient settings compared with community rates. *J Gerontol A Biol Sci Med Sci* 2000;55:M522–6.
201. Centers for Medicare and Medicaid Services. Medicare and Medicaid programs; conditions of participation: immunization standards for hospitals, long-term care facilities, and home health agencies. *Federal Register* 2002;67:61808–14.
202. Fedson DS, Wajda A, Nicol JP, Roos LL. Disparity between influenza vaccination rates and risks for influenza-associated hospital discharge and death in Manitoba in 1982–1983. *Ann Intern Med* 1992;116:550–5.
203. Bratzler DW, Houck PM, Jiang H, et al. Failure to vaccinate Medicare inpatients: a missed opportunity. *Arch Intern Med* 2002;162:2349–56.
204. Fedson DS, Houck P, Bratzler D. Hospital-based influenza and pneumococcal vaccination: Sutton's Law applied to prevention. *Infect Control Hosp Epidemiol* 2000;21:692–9.
205. CDC. Delayed supply of influenza vaccine and adjunct ACIP influenza vaccine recommendations for the 2000–01 influenza season [Notice to readers]. *MMWR* 2000;49:619–22.
206. CDC. Influenza activity—United States, 2001–02 season. *MMWR* 2001;50:1084–6.
207. CDC. Delayed influenza vaccine availability for 2001–02 season and supplemental recommendations of the Advisory Committee on Immunization Practices. *MMWR* 2001;50:582–5.
208. Kendal AP, Maassab HF, Alexandrova GI, Ghendon YZ. Development of cold-adapted recombinant live, attenuated influenza A vaccines in the U.S.A. and U.S.S.R. *Antiviral Res* 1981;1:339–65.
209. Maassab HF, DeBorde DC. Development and characterization of cold-adapted viruses for use as live virus vaccines. *Vaccine* 1985;3:355–69.
210. Murphy BR. Use of live attenuated cold-adapted influenza reassortant virus vaccines in infants, children, young adults, and elderly adults. *Infect Dis Clin Pract* 1993;2:174–81.
211. Potter CW. Attenuated influenza virus vaccines. *Rev Med Virol* 1994;4:279–92.
212. Clements ML, Stephens I. New and improved vaccines against influenza. *New Gen Vac* 1997;2<sup>nd</sup> ed.:545–70.
213. Edwards KM, Dupont WD, Westrich MK, Plummer WD Jr, Palmer PS, Wright PF. Randomized controlled trial of cold-adapted and inactivated vaccines for the prevention of influenza A disease. *J Infect Dis* 1994;169:68–76.
214. Belshe RB, Mendelman PM, Treanor J, et al. Efficacy of live attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine in children. *N Engl J Med* 1998;338:1405–12.
215. Belshe RB, Gruber WC, Mendelman PM, et al. Efficacy of vaccination with live attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine against a variant (A/Sydney) not contained in the vaccine. *J Pediatr* 2000;136:168–75.
216. Nichol KL, Mendelman PM, Mallon KP, et al. Effectiveness of live, attenuated intranasal influenza virus vaccine in healthy, working adults: a randomized controlled trial. *JAMA* 1999;282:137–44.
217. American Academy of Pediatrics. Influenza. In: Pickering LK, editor. 2000 red book: report of the Committee on Infectious Diseases. Elk Grove Village, IL: American Academy of Pediatrics, 2000:351–9.
218. Schmid ML, Kudesia G, Wake S, Read RC. Prospective comparative study of culture specimens and methods in diagnosing influenza in adults. *BMJ* 1998;316:275.
219. Medical Letter, Inc. Rapid diagnostic tests for influenza. *Medical Letter* 1999;41:121–2.
220. Storch GA. Rapid diagnostic tests for influenza. *Curr Opin Pediatr* 2003;15:77–84.
221. Uyeki TM. Influenza diagnosis and treatment in children: a review of studies on clinically useful tests and antiviral treatment for influenza. *Pediatr Infect Dis J* 2003;22:164–77.
222. Tominack RL, Hayden FG. Rimantadine hydrochloride and amantadine hydrochloride use in influenza A virus infections. *Infect Dis Clin North Am* 1987;1:459–78.
223. Hayden FG, Osterhaus AD, Treanor JJ, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza virus infections. GG167 Influenza Study Group. *N Engl J Med* 1997;337:874–80.
224. MIST (Management of Influenza in the Southern Hemisphere Trialists). Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. The MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group. *Lancet* 1998;352:1877–81.
225. Makela MJ, Pauksens K, Rostila T, et al. Clinical efficacy and safety of the orally inhaled neuraminidase inhibitor zanamivir in the treatment of influenza: a randomized, double-blind, placebo-controlled European study. *J Infect* 2000;40:42–8.
226. Matsumoto K, Ogawa N, Nerome K, et al. Safety and efficacy of the neuraminidase inhibitor zanamivir in treating influenza virus infection in adults: results from Japan. GG167 Group. *Antivir Ther* 1999;4:61–8.
227. Monto AS, Fleming DM, Henry D, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenza A and B virus infections. *J Infect Dis* 1999;180:254–61.
228. Lalezari J, Campion K, Keene O, Silagy C. Zanamivir for the treatment of influenza A and B infection in high-risk patients: a pooled analysis of randomized controlled trials. *Arch Intern Med* 2001;161:212–7.
229. Treanor JJ, Hayden FG, Vrooman PS, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: a randomized controlled trial. US Oral Neuraminidase Study Group. *JAMA* 2000;283:1016–24.

230. Nicholson KG, Aoki FY, Osterhaus AD, et al. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. *Neuraminidase Inhibitor Flu Treatment Investigator Group. Lancet* 2000;355:1845–50.
231. Hendrick JA, Barzilai A, Behre U. Zanamivir for treatment of symptomatic influenza A and B infection in children five to twelve years of age: a randomized controlled trial. *Pediatr Infect Dis J* 2000;19:410–7.
232. Whitley RJ, Hayden FG, Reisinger KS, et al. Oral oseltamivir treatment of influenza in children. *Pediatr Infect Dis J* 2001;20:127–33.
233. Glaxo Wellcome, Inc. Relenza® (zanamivir for inhalation) [Product information]. Research Triangle Park, NC: Glaxo Wellcome, Inc., 2001.
234. Roche Laboratories Inc. Tamiflu™ (oseltamivir phosphate) capsules [Product information]. Nutley, NJ: Roche Laboratories, Inc., 2000.
235. Murphy KR, Eivindson A, Pauksens K, et al. Efficacy and safety of inhaled zanamivir for the treatment of influenza in patients with asthma or chronic obstructive pulmonary disease: a double-blind, randomised, placebo-controlled, multicentre study. *Clin Drug Invest* 2000;20:337–49.
236. Uyeki T, Winquist A. Influenza. *Clin Evid* 2002;645–51.
237. Osterhaus ADM, Makela MJ, Webster A, Keene ON. Efficacy of inhaled zanamivir in the treatment of influenza B [Abstract 281]. Abstracts of the 39<sup>th</sup> Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC: American Society for Microbiology. 1999:420.
238. Bardsley-Elliott A, Noble S. Oseltamivir. *Drugs* 1999;58:851–60.
239. Welliver R, Monto AS, Carewicz O, et al. Effectiveness of oseltamivir in preventing influenza in household contacts: a randomized controlled trial. *JAMA* 2001;285:748–54.
240. Hayden FG, Jennings L, Robson R, et al. Oral oseltamivir in human experimental influenza B infection. *Antivir Ther* 2000;5:205–13.
241. Woods JM, Bethell RC, Coates JA, et al. 4-Guanidino-2,4-dideoxy-2,3-dehydro-N-acetylneuraminic acid is a highly effective inhibitor both of the sialidase (neuraminidase) and of growth of a wide range of influenza A and B viruses in vitro. *Antimicrob Agents Chemother* 1993;37:1473–9.
242. Hayden FG, Rollins BS, Madren LK. Anti-influenza virus activity of the neuraminidase inhibitor 4-guanidino-Neu5Ac2en in cell culture and in human respiratory epithelium. *Antiviral Res* 1994;25:123–31.
243. Mendel DB, Tai CY, Escarpe PA, Li W, et al. Oral administration of a prodrug of the influenza virus neuraminidase inhibitor GS 4071 protects mice and ferrets against influenza infection. *Antimicrob Agents Chemother* 1998;42:640–6.
244. Sidwell RW, Huffman JH, Barnard DL, et al. Inhibition of influenza virus infections in mice by GS4104, an orally effective influenza virus neuraminidase inhibitor. *Antiviral Res* 1998;37:107–20.
245. Hayden FG, Rollins BS. In vitro activity of the neuraminidase inhibitor GS4071 against influenza viruses [Abstract 159]. *Antiviral Res* 1997;34:A86.
246. Mendel DB, Tai CY, Escarpe PA et al. GS 4071 is a potent and selective inhibitor of the growth and neuraminidase activity of influenza A and B viruses in vitro [Abstract 111]. *Antiviral Res* 1997;34:A73.
247. Ryan DM, Ticehurst J, Dempsey MH, Penn CR. Inhibition of influenza virus replication in mice by GG167 (4-guanidino-2,4-dideoxy-2,3-dehydro-N-acetylneuraminic acid) is consistent with extracellular activity of viral neuraminidase (sialidase). *Antimicrob Agents Chemother* 1994;38:2270–75.
248. Ryan DM, Ticehurst J, Dempsey MH. GG167 (4-guanidino-2,4-dideoxy-2,3-dehydro-N-acetylneuraminic acid) is a potent inhibitor of influenza virus in ferrets. *Antimicrob Agents Chemother* 1995;39:2583–4.
249. Food and Drug Administration. Subject: safe and appropriate use of influenza drugs [Public Health Advisory]. Rockville, MD: US Department of Health and Human Services, Food and Drug Administration, 2000.
250. Nicholson KG. Use of antivirals in influenza in the elderly: prophylaxis and therapy. *Gerontology* 1996;42:280–9.
251. Wintermeyer SM, Nahata MC. Rimantadine: a clinical perspective. *Ann Pharmacother* 1995;29:299–310.
252. Martin C, Mahoney P, Ward P. Oral oseltamivir reduces febrile illness in patients considered at high risk of influenza complications [Abstract W22-7]. In: *Options for the control of Influenza IV*. New York, NY: Excerpta Medica, 2001:807–11.
253. Gravenstein S, Johnston SL, Loeschel E, Webster A. Zanamivir: a review of clinical safety in individuals at high risk of developing influenza-related complications. *Drug Saf* 2001;24:1113–25.
254. Bowles SK, Lee W, Simor AE, et al. Use of oseltamivir during influenza outbreaks in Ontario nursing homes, 1999–2000. *J Am Geriatr Soc* 2002;50:608–16.
255. Thompson J, Fleet W, Lawrence E, Pierce E, Morris L, Wright P. Comparison of acetaminophen and rimantadine in the treatment of influenza A infection in children. *J Med Virol* 1987;21:249–55.
256. Hall CB, Dolin R, Gala CL, et al. Children with influenza A infection: treatment with rimantadine. *Pediatrics* 1987;80:275–82.
257. Guay DR. Amantadine and rimantadine prophylaxis of influenza A in nursing homes: a tolerability perspective. *Drugs Aging* 1994;5:8–19.
258. Patriarca PA, Kater NA, Kendal AP, Bregman DJ, Smith JD, Sikes RK. Safety of prolonged administration of rimantadine hydrochloride in the prophylaxis of influenza A virus infections in nursing homes. *Antimicrob Agents Chemother* 1984;26:101–3.
259. Arden NH, Patriarca PA, Fasano MB, et al. Roles of vaccination and amantadine prophylaxis in controlling an outbreak of influenza A (H3N2) in a nursing home. *Arch Intern Med* 1988;148:865–8.
260. Monto AS, Robinson DP, Herlocher ML, Hinson JM, Elliott MJ, Crisp A. Zanamivir in the prevention of influenza among healthy adults: a randomized controlled trial. *JAMA* 1999;282:31–5.
261. Hayden FG, Atmar RL, Schilling M, et al. Use of the selective oral neuraminidase inhibitor oseltamivir to prevent influenza. *N Engl J Med* 1999;341:1336–43.
262. Monto AS, Pichichero ME, Blanckenberg SJ, et al. Zanamivir prophylaxis: an effective strategy for the prevention of influenza types A and B within households. *J Infect Dis* 2002;186:1582–8.
263. Hayden FG, Gubareva LV, Monto AS, et al. Inhaled zanamivir for the prevention of influenza in families. *N Engl J Med* 2000;343:1282–9.
264. Schilling M, Povinelli L, Krause P, et al. Efficacy of zanamivir for chemoprophylaxis of nursing home influenza outbreaks. *Vaccine* 1998;16:1771–4.
265. Lee C, Loeb M, Phillips A, et al. Zanamivir use during transmission of amantadine-resistant influenza A in a nursing home. *Infect Control Hosp Epidemiol* 2000;21:700–4.
266. Parker R, Loewen N, Skowronski D. Experience with oseltamivir in the control of a nursing home influenza B outbreak. *Can Commun Dis Rep* 2001;27:37–40.

267. Peters PH Jr., Gravenstein S, Norwood P, et al. Long-term use of oseltamivir for the prophylaxis of influenza in a vaccinated frail older population. *J Am Geriatr Soc* 2001;49:1025–31.
268. Webster A, Boyce M, Edmundson S, Miller I. Coadministration of orally inhaled zanamivir with inactivated trivalent influenza vaccine does not adversely affect the production of antihaemagglutinin antibodies in the serum of healthy volunteers. *Clin Pharmacokinet* 1999;36(Suppl 1):51–8.
269. Patriarca PA, Arden NH, Koplan JP, Goodman RA. Prevention and control of type A influenza infections in nursing homes: benefits and costs of four approaches using vaccination and amantadine. *Ann Intern Med* 1987;107:732–40.
270. Gomolin IH, Leib HB, Arden NH, Sherman FT. Control of influenza outbreaks in the nursing home: guidelines for diagnosis and management. *J Am Geriatr Soc* 1995;43:71–4.
271. Garner JS. Guideline for isolation precautions in hospitals. Hospital Infection Control Practices Advisory Committee. *Infect Control Hosp Epidemiol* 1996;17:53–80.
272. Bradley SF. Prevention of influenza in long-term-care facilities. Long-Term-Care Committee of the Society for Healthcare Epidemiology of America. *Infect Control Hosp Epidemiol* 1999;20:629–37.
273. Shijubo N, Yamada G, Takahashi M, Tokunoh T, Suzuki T, Abe S. Experience with oseltamivir in the control of nursing home influenza A outbreak. *Intern Med* 2002;41:366–70.
274. Forest Pharmaceuticals. Flumadine<sup>®</sup> syrup (rimantadine hydrochloride syrup) [Package insert]. St. Louis, MO: Forest Pharmaceuticals, 2001.
275. Keyser LA, Karl M, Nafziger AN, Bertino JS Jr. Comparison of central nervous system adverse effects of amantadine and rimantadine used as sequential prophylaxis of influenza A in elderly nursing home patients. *Arch Intern Med* 2000;160:1485–8.
276. Endo Pharmaceuticals Inc. Symmetrel [Package insert]. Dayton, NJ: Endo Pharmaceuticals, Inc., 2000.
277. Soung LS, Ing TS, Daugirdas JT, et al. Amantadine hydrochloride pharmacokinetics in hemodialysis patients. *Ann Intern Med* 1980;93:46–9.
278. Capparelli EV, Stevens RC, Chow MS, Izard M, Wills RJ. Rimantadine pharmacokinetics in healthy subjects and patients with end-stage renal failure. *Clin Pharmacol Ther* 1988;43:536–41.
279. Cass LM, Efthymiopoulos C, Marsh J, Bye A. Effect of renal impairment on the pharmacokinetics of intravenous zanamivir. *Clin Pharmacokinet* 1999;36(Suppl 1):13–9.
280. Calfee DP, Peng AW, Cass LM, Lobo M, Hayden FG. Safety and efficacy of intravenous zanamivir in preventing experimental human influenza A virus infection. *Antimicrob Agents Chemother* 1999;43:1616–20.
281. Cass LM, Efthymiopoulos C, Bye A. Pharmacokinetics of zanamivir after intravenous, oral, inhaled or intranasal administration to healthy volunteers. *Clin Pharmacokinet* 1999;36(Suppl 1):1–11.
282. Schnack H, Wewalka F, Guttman G. Liver function during amantadine hydrochloride medication in compensated liver disease. *Int Z Klin Pharmakol Ther Toxikol* 1969;2:185–7.
283. Atkinson WL, Arden NH, Patriarca PA, Leslie N, Lui KJ, Gohd R. Amantadine prophylaxis during an institutional outbreak of type A (H1N1) influenza. *Arch Intern Med* 1986;146:1751–6.
284. Soo W. Adverse effects of rimantadine: summary from clinical trials. *J Respir Dis* 1989;10(Suppl):S26–31.
285. Bleidner WE, Harmon JB, Hewes WE, Lynes TE, Hermann EC. Absorption, distribution and excretion of amantadine hydrochloride. *J Pharmacol Exp Ther* 1965;150:484–90.
286. Douglas RG. Prophylaxis and Treatment of Influenza. *N Engl J Med* 1990;322:443–50.
287. Aoki FY, Sitar DS. Amantadine kinetics in healthy elderly men: implications for influenza prevention. *Clin Pharmacol Ther* 1985;37:137–44.
288. Aoki FY, Sitar DS. Clinical pharmacokinetics of amantadine hydrochloride. *Clin Pharmacokinet* 1988;14:35–51.
289. Wills RJ, Belshe R, Tomlins D, et al. Pharmacokinetics of rimantadine hydrochloride in patients with chronic liver disease. *Clin Pharmacol Ther* 1987;42:449–54.
290. Wills RJ. Update on rimantadine's clinical pharmacokinetics. *J Respir Dis* 1989;(Suppl):S20–5.
291. Cass LM, Brown J, Pickford M, et al. Pharmacoscintigraphic evaluation of lung deposition of inhaled zanamivir in healthy volunteers. *Clin Pharmacokinet* 1999;36(Suppl 1):21–31.
292. He G, Massarella J, Ward P. Clinical pharmacokinetics of the prodrug oseltamivir and its active metabolite Ro 64-0802. *Clin Pharmacokinet* 1999;37:471–84.
293. Dolin R, Reichman RC, Madore HP, Maynard R, Linton PN, Webber-Jones J. Controlled trial of amantadine and rimantadine in the prophylaxis of influenza A infection. *N Engl J Med* 1982;307:580–4.
294. Hayden FG, Treanor JJ, Fritz RS, et al. Use of the oral neuraminidase inhibitor oseltamivir in experimental human influenza: randomized controlled trials for prevention and treatment. *JAMA* 1999;282:1240–6.
295. Daniel MJ, Barnett JM, Pearson BA. Low potential for drug interactions with zanamivir. *Clin Pharmacokinet* 1999;36(Suppl 1):41–50.
296. Belshe RB, Smith MH, Hall CB, Betts R, Hay AJ. Genetic basis of resistance to rimantadine emerging during treatment of influenza virus infection. *J Virol* 1988;62:1508–12.
297. Hayden FG, Sperber SJ, Belshe RB, Clover RD, Hay AJ, Pyke S. Recovery of drug-resistant influenza A virus during therapeutic use of rimantadine. *Antimicrob Agents Chemother* 1991;35:1741–7.
298. Saito R, Oshitani H, Masuda H, Suzuki H. Detection of amantadine-resistant influenza A virus strains in nursing homes by PCR-restriction fragment length polymorphism analysis with nasopharyngeal swabs. *J Clin Microbiol* 2002;40:84–8.
299. Houck P, Hemphill M, LaCroix S, Hirsh D, Cox N. Amantadine-resistant influenza A in nursing homes: identification of a resistant virus prior to drug use. *Arch Intern Med* 1995;155:533–7.
300. Hayden FG, Belshe RB, Clover RD, Hay AJ, Oakes MG, Soo W. Emergence and apparent transmission of rimantadine-resistant influenza A virus in families. *N Engl J Med* 1989;321:1696–1702.
301. Mast EE, Harmon MW, Gravenstein S, et al. Emergence and possible transmission of amantadine-resistant viruses during nursing home outbreaks of influenza A (H3N2). *Am J Epidemiol* 1991;134:988–97.
302. Hayden FG, Hay AJ. Emergence and transmission of influenza A viruses resistant to amantadine and rimantadine. *Curr Top Microbiol Immunol* 1992;176:119–30.
303. Degelau J, Somani SK, Cooper SL, Guay DR, Crossley KB. Amantadine-resistant influenza A in a nursing facility. *Arch Intern Med* 1992;152:390–2.

304. Ziegler T, Hemphill ML, Ziegler ML, et al. Low incidence of rimantadine resistance in field isolates of influenza A viruses. *J Infect Dis* 1999;180:935–9.
305. Gubareva LV, Robinson MJ, Bethell RC, Webster RG. Catalytic and framework mutations in the neuraminidase active site of influenza viruses that are resistant to 4-guanidino-Neu5Ac2en. *J Virol* 1997;71:3385–90.
306. Colacino JM, Laver WG, Air GM. Selection of influenza A and B viruses for resistance to 4-guanidino-Neu5Ac2en in cell culture. *J Infect Dis* 1997;176(Suppl 1):S66–8.
307. Gubareva LV, Bethell R, Hart GJ, Murti KG, Penn CR, Webster RG. Characterization of mutants of influenza A virus selected with the neuraminidase inhibitor 4-guanidino-Neu5Ac2en. *J Virol* 1996;70:1818–27.
308. Blick TJ, Tiong T, Sahasrabudhe A, et al. Generation and characterization of an influenza virus neuraminidase variant with decreased sensitivity to the neuraminidase-specific inhibitor 4-guanidino-Neu5Ac2en. *Virology* 1995;214:475–84.
309. McKimm-Breschkin JL, Blick TJ, Sahasrabudhe A, et al. Generation and characterization of variants of NWS/G70C influenza virus after in vitro passage in 4-amino-Neu5Ac2en and 4-guanidino-Neu5Ac2en. *Antimicrob Agents Chemother* 1996;40:40–6.
310. Staschke KA, Colacino JM, Baxter AJ, et al. Molecular basis for the resistance of influenza viruses to 4-guanidino-Neu5Ac2en. *Virology* 1995;214:642–6.
311. McKimm-Breschkin JL, Sahasrabudhe A, Blick TJ, et al. Mutations in a conserved residue in the influenza virus neuraminidase active site decreases sensitivity to Neu5Ac2en-derived inhibitors. *J Virol* 1998;72:2456–62.
312. Tai CY, Escarpe PA, Sidwell RW, et al. Characterization of human influenza virus variants selected in vitro in the presence of the neuraminidase inhibitor GS 4071. *Antimicrob Agents Chemother* 1998;42:3234–41.
313. Hay AJ, Wolstenholme AJ, Skehel JJ, Smith MH. Molecular basis of the specific anti-influenza action of amantadine. *EMBO J* 1985;4:3021–4.
314. Appleyard G. Amantadine-resistance as a genetic marker for influenza viruses. *J Gen Virol* 1977;36:249–55.
315. Barnett JM, Cadman A, Gor D, et al. Zanamivir susceptibility monitoring and characterization of influenza virus clinical isolates obtained during phase II clinical efficacy studies. *Antimicrob Agents Chemother* 2000;44:78–87.
316. Gubareva LV, Matrosovich MN, Brenner MK, Bethell RC, Webster RG. Evidence for zanamivir resistance in an immunocompromised child infected with influenza B virus. *J Infect Dis* 1998;178:1257–62.
317. Gubareva LV, Kaiser L, Matrosovich MN, Soo-Hoo Y, Hayden FG. Selection of influenza virus mutants in experimentally infected volunteers treated with oseltamivir. *J Infect Dis* 2001;183:523–31.
318. Jackson HC, Roberts N, Wang ZM, Belshe R. Management of influenza: use of new antivirals and resistance in perspective. *Clin Drug Invest* 2000;20:447–54.
319. Tisdale M. Monitoring of viral susceptibility: new challenges with the development of influenza NA inhibitors. *Rev Med Virol* 2000;10:45–55.
320. Gubareva LV, Webster RG, Hayden FG. Detection of influenza virus resistance to neuraminidase inhibitors by an enzyme inhibition assay. *Antiviral Res* 2002;53:47–61.
321. Zambon M, Hayden FG. Position statement: global neuraminidase inhibitor susceptibility network. *Antiviral Res* 2001;49:147–56.









# MMWR™

## Morbidity and Mortality Weekly Report

Recommendations and Reports

April 25, 2003 / Vol. 52 / No. RR-8

### Continuing Education Activity Sponsored by CDC Prevention and Control of Influenza Recommendations of the Advisory Committee on Immunization Practices (ACIP)

**EXPIRATION — April 25, 2004**

You must complete and return the response form electronically or by mail by **April 25, 2004**, to receive continuing education credit. If you answer all of the questions, you will receive an award letter for 2.0 hours Continuing Medical Education (CME) credit; 0.2 Continuing Education Units (CEUs);

or 2.3 contact hours Continuing Nursing Education (CNE) credit. If you return the form electronically, you will receive educational credit immediately. If you mail the form, you will receive educational credit in approximately 30 days. No fees are charged for participating in this continuing education activity.

#### INSTRUCTIONS

##### By Internet

1. Read this *MMWR* (Vol. 52, RR-8), which contains the correct answers to the questions beginning on the next page.
2. Go to the *MMWR* Continuing Education Internet site at <<http://www.cdc.gov/mmwr/cme/conted.html>>.
3. Select which exam you want to take and select whether you want to register for CME, CEU, or CNE credit.
4. Fill out and submit the registration form.
5. Select exam questions. To receive continuing education credit, you must answer all of the questions. Questions with more than one correct answer will instruct you to "Indicate all that apply."
6. Submit your answers no later than **April 25, 2004**.
7. Immediately print your Certificate of Completion for your records.

##### By Mail or Fax

1. Read this *MMWR* (Vol. 52, RR-8), which contains the correct answers to the questions beginning on the next page.
2. Complete all registration information on the response form, including your name, mailing address, phone number, and e-mail address, if available.
3. Indicate whether you are registering for CME, CEU, or CNE credit.
4. Select your answers to the questions, and mark the corresponding letters on the response form. To receive continuing education credit, you must answer all of the questions. Questions with more than one correct answer will instruct you to "Indicate all that apply."
5. Sign and date the response form or a photocopy of the form and send no later than **April 25, 2004**, to  
Fax: 404-639-4198 Mail: MMWR CE Credit  
Office of Scientific and Health Communications  
Epidemiology Program Office, MS C-08  
Centers for Disease Control and Prevention  
1600 Clifton Rd, N.E.  
Atlanta, GA 30333
6. Your Certificate of Completion will be mailed to you within 30 days.

#### ACCREDITATION

**Continuing Medical Education (CME).** CDC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. CDC designates this educational activity for a maximum of 2.0 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

**Continuing Education Unit (CEU).** CDC has been approved as an authorized provider of continuing education and training programs by the International Association for Continuing Education and Training and awards 0.2 Continuing Education Units (CEUs).

**Continuing Nursing Education (CNE).** This activity for 2.3 contact hours is provided by CDC, which is accredited as a provider of continuing education in nursing by the American Nurses Credentialing Center's Commission on Accreditation.

**CENTERS FOR DISEASE CONTROL AND PREVENTION**

**SAFER • HEALTHIER • PEOPLE™**

## Goal and Objectives

This *MMWR* provides recommendations for using influenza vaccine and influenza antiviral agents in the United States. These recommendations were developed by CDC staff members and the Influenza Working Group of the Advisory Committee on Immunization Practices (ACIP). The goal of this report is to provide guidance for health-care professionals regarding administration of influenza vaccine and antiviral agents in the United States. Upon completion of this educational activity, the reader should be able to 1) specify the time span in which ACIP recommends administering the influenza vaccine for each influenza season; 2) identify the primary target groups for annual influenza vaccination; 3) describe one strategy for implementing ACIP recommendations for influenza vaccination among a patient population; and 4) recognize the uses of antiviral drugs as an adjunct to vaccination in the prevention and control of influenza.

**To receive continuing education credit, please answer all of the following questions.**

1. **In the United States, the annual influenza vaccine should be administered . . .**
  - A. to health-care workers and those at high risk for complications from influenza, beginning in October.
  - B. to children who are aged <9 years who are receiving the vaccine for the first time, beginning in October.
  - C. to household contacts of children aged <2 years, beginning in October.
  - D. as long as the influenza season lasts and vaccine is available.
  - E. all of the above.
2. **Pregnant women should receive influenza vaccine . . .**
  - A. in the second trimester only.
  - B. in accordance with ACIP recommendations and the assessment of their health-care providers.
  - C. in the third trimester of pregnancy.
  - D. never.
  - E. after delivery.
3. **When using antiviral drugs for chemoprophylaxis of influenza in a nursing home, they should be administered . . .**
  - A. for 1 week after the end of the outbreak or until the influenza season peaks.
  - B. only to residents who have not been vaccinated.
  - C. for  $\geq 2$  weeks.
  - D. for a minimum of 2 weeks or 1 week after the end of the outbreak.
  - E. to employees in direct contact with the residents.
4. **Influenza vaccination is recommended for persons aged 50–64 years because . . .**
  - A. persons in this age group display a decrease in immune function.
  - B. an increase in morbidity and mortality as a result of complications of influenza is related to age in this group.
  - C. a high proportion of persons in this age group have  $\geq 1$  condition that puts them at high risk for complications of influenza.
  - D. none of the above.
  - E. all of the above.
5. **Because young, otherwise healthy children are at increased risk for influenza-related hospitalizations, ACIP . . .**
  - A. encourages influenza vaccine for children aged 6–23 months.
  - B. recommends influenza vaccine for children aged <6 months who have  $\geq 1$  condition that puts them at high risk for complications.
  - C. recommends vaccination of household contacts of children aged 6–23 months.
  - D. B and C.
  - E. A and C.
6. **Use of the antiviral drugs amantadine and rimantadine in the treatment of influenza . . .**
  - A. provides potential for emergence of antiviral-resistant viruses.
  - B. can reduce the duration of illness from infection with influenza A virus.
  - C. should be administered within 72 hours of onset of symptoms.
  - D. A and B.
  - E. A and C.
7. **ACIP . . .**
  - A. encourages using standing orders in long-term-care facilities only.
  - B. recommends using standing orders in long-term-care facilities and encourages using standing orders in correctional facilities and physicians' offices.
  - C. recommends using standing orders in hospitals and by home health agencies.
  - D. A and B.
  - E. B and C.
8. **Which of the following conditions is a valid contraindication for use of influenza vaccine?**
  - A. Severe allergy to a component of the vaccine.
  - B. Concurrent administration of pneumococcal vaccine.
  - C. Recent administration of antibody-containing blood product (e.g., whole blood or immunoglobulin).
  - D. Sore throat.
  - E. All of the above.
9. **Which of the following are within the target groups for annual influenza vaccination?**
  - A. Teenagers with diabetes mellitus.
  - B. Persons aged  $\geq 50$  years.
  - C. Medical assistants.
  - D. Adults with reactive airway disorder.
  - E. All of the above.
10. **What is the most common adverse reaction after influenza vaccination?**
  - A. Soreness at the injection site.
  - B. Allergic reaction.
  - C. Influenza-like illness.
  - D. Fever.
  - E. Guillain-Barré syndrome.
11. **Implementation of ACIP recommendations for annual influenza vaccine can be enhanced by . . .**
  - A. identifying patients who are in the target population for vaccination.
  - B. reminding patients by mail, telephone, or other means that they are in a target group to receive influenza vaccine.
  - C. offering vaccination during health-care encounters, beginning in September.
  - D. A and B only.
  - E. A, B, and C.
12. **Indicate your work setting.**
  - A. State/local health department.
  - B. Other public health setting.
  - C. Hospital clinic/private practice.
  - D. Managed care organization.
  - E. Academic institution.
  - F. Other.



13. Which best describes your professional activities?
- A. Patient care — emergency/urgent care department.
  - B. Patient care — inpatient.
  - C. Patient care — primary-care clinic or office.
  - D. Laboratory/pharmacy.
  - E. Public health.
  - F. Other.
14. I plan to use these recommendations as the basis for . . . (Indicate all that apply.)
- A. health education materials.
  - B. insurance reimbursement policies.
  - C. local practice guidelines.
  - D. public policy.
  - E. other.
15. During influenza season, approximately how many influenza vaccinations do you administer?
- A. None.
  - B. 1–5.
  - C. 6–20.
  - D. 21–50.
  - E. 51–100.
  - F. >100.
16. How much time did you spend reading this report and completing the exam?
- A. 1–1.5 hours.
  - B. >1.5 hours but <2 hours.
  - C. 2–2.5 hours.
  - D. >2.5 hours.

17. After reading this report, I am confident I can specify the time span in which ACIP recommends administering the influenza vaccine for each influenza season.
- A. Strongly agree.
  - B. Agree.
  - C. Neither agree nor disagree.
  - D. Disagree.
  - E. Strongly disagree.
18. After reading this report, I am confident I can identify the primary target groups for annual influenza vaccination.
- A. Strongly agree.
  - B. Agree.
  - C. Neither agree nor disagree.
  - D. Disagree.
  - E. Strongly disagree.
19. After reading this report, I am confident I can describe one strategy for implementing ACIP recommendations for influenza vaccination among a patient population.
- A. Strongly agree.
  - B. Agree.
  - C. Neither agree nor disagree.
  - D. Disagree.
  - E. Strongly disagree.

(Continued on pg CE-4)

Detach or photocopy.

**MMWR Response Form for Continuing Education Credit**  
**April 25, 2003/Vol. 52/No. RR-8**  
**Prevention and Control of Influenza**  
**Recommendations of the Advisory Committee**  
**on Immunization Practices (ACIP)**

To receive continuing education credit, you must  
 1. provide your contact information;  
 2. indicate your choice of CME, CEU, or CNE credit;  
 3. answer all of the test questions;  
 4. sign and date this form or a photocopy;  
 5. submit your answer form by April 25, 2004.  
 Failure to complete these items can result in a delay or rejection of your application for continuing education credit.

Check One  
 CME Credit  
 CEU Credit  
 CNE Credit

Last Name \_\_\_\_\_ First Name \_\_\_\_\_  
 Street Address or P.O. Box \_\_\_\_\_  
 Apartment \_\_\_\_\_ or Suite \_\_\_\_\_  
 City \_\_\_\_\_ State \_\_\_\_\_ ZIP Code \_\_\_\_\_  
 Phone Number \_\_\_\_\_ Fax Number \_\_\_\_\_  
 E-Mail Address \_\_\_\_\_

Fill in the appropriate blocks to indicate your answers. Remember, you must answer all of the questions to receive continuing education credit!

1. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F  
 2. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F  
 3. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F  
 4. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F  
 5. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F  
 6. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F  
 7. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F  
 8. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F  
 9. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F  
 10. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F  
 11. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F  
 12. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F  
 13. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F  
 14. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F  
 15. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F  
 16. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F  
 17. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F  
 18. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F  
 19. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F  
 20. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F  
 21. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F  
 22. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F  
 23. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F  
 24. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F  
 25. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F  
 26. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F  
 27. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F

Signature \_\_\_\_\_ Date I Completed Exam \_\_\_\_\_

- 20. After reading this report, I am confident I can recognize the uses of antiviral drugs as an adjunct to vaccination in the prevention and control of influenza.**
- A. Strongly agree.
  - B. Agree.
  - C. Neither agree nor disagree.
  - D. Disagree.
  - E. Strongly disagree.
- 21. The objectives are relevant to the goal of this report.**
- A. Strongly agree.
  - B. Agree.
  - C. Neither agree nor disagree.
  - D. Disagree.
  - E. Strongly disagree.
- 22. The teaching strategies used in this report (text and tables) were useful.**
- A. Strongly agree.
  - B. Agree.
  - C. Neither agree nor disagree.
  - D. Disagree.
  - E. Strongly disagree.
- 23. Overall, the presentation of the report enhanced my ability to understand the material.**
- A. Strongly agree.
  - B. Agree.
  - C. Neither agree nor disagree.
  - D. Disagree.
  - E. Strongly disagree.
- 24. These recommendations will affect my practice.**
- A. Strongly agree.
  - B. Agree.
  - C. Neither agree nor disagree.
  - D. Disagree.
  - E. Strongly disagree.
- 25. The content of this activity was appropriate for my educational needs.**
- A. Strongly agree.
  - B. Agree.
  - C. Neither agree nor disagree.
  - D. Disagree.
  - E. Strongly disagree.
- 26. The availability of continuing education credit influenced my decision to read this report.**
- A. Strongly agree.
  - B. Agree.
  - C. Neither agree nor disagree.
  - D. Disagree.
  - E. Strongly disagree.
- 27. How did you learn about this continuing education activity?**
- A. Internet.
  - B. Advertisement (e.g., fact sheet, *MMWR* cover, newsletter, or journal).
  - C. Coworker/supervisor.
  - D. Conference presentation.
  - E. *MMWR* subscription.
  - F. Other.

Correct answers for questions 1–11.  
1. E; 2. B; 3. D; 4. C; 5. E; 6. D; 7. E; 8. A; 9. E; 10. A; 11. E.

## **Advisory Committee on Immunization Practices Membership List, February 2003**

**Chairman:** John F. Modlin, M.D., Professor of Pediatrics and Medicine, Dartmouth Medical School, Lebanon, New Hampshire.

**Executive Secretary:** Dixie E. Snider, Jr., M.D., Associate Director for Science, Centers for Disease Control and Prevention, Atlanta, Georgia.

**Members:** Guthrie S. Birkhead, M.D., New York State Department of Health, Albany, New York; Dennis A. Brooks, M.D., Johnson Medical Center, Baltimore, Maryland; Jaime Deseda-Tous, M.D., San Jorge Children's Hospital, San Juan, Puerto Rico; Celine I. Hanson, M.D., Texas Department of Health, Austin, Texas; Myron J. Levin, M.D., University of Colorado School of Medicine, Denver, Colorado; Paul A. Offit, M.D., Children's Hospital of Philadelphia, Philadelphia, Pennsylvania; Margaret B. Rennels, M.D., University of Maryland School of Medicine, Baltimore, Maryland; John E. Salamone, Washington, D.C.; Lucy S. Tompkins, M.D., Ph.D., Stanford University Medical Center, Stanford, California; Bonnie M. Word, M.D., Monmouth Junction, New Jersey; and Richard Zimmerman, M.D., University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania.

**Ex-Officio Members:** James E. Cheek, M.D., Indian Health Service, Albuquerque, New Mexico; Col. Benedict M. Diniega, M.D., Department of Defense, Falls Church, Virginia; Geoffrey S. Evans, M.D., Health Resources and Services Administration, Rockville, Maryland; Bruce Gellin, M.D., National Vaccine Program Office, Washington, D.C.; T. Randolph Graydon, Centers for Medicare and Medicaid Services, Baltimore, Maryland; Carole Heilman, Ph.D., National Institutes of Health, Bethesda, Maryland; Karen Midthun, M.D., Food and Drug Administration, Bethesda, Maryland; and Kristin Lee Nichol, M.D., Veterans Administration Medical Center, Minneapolis, Minnesota.

**Liaison Representatives:** American Academy of Family Physicians, Richard D. Clover, M.D., Louisville, Kentucky, and Martin Mahoney, M.D., Ph.D., Clarence, New York; American Academy of Pediatrics, Jon Abramson, M.D., Winston-Salem, North Carolina, and Carol Baker, M.D., Houston, Texas; American Association of Health Plans, Robert Scallettar, M.D., North Haven, Connecticut; American College Health Association, James C. Turner, M.D., Charlottesville, North Carolina; American College of Physicians, Kathleen M. Neuzil, M.D., Seattle, Washington; American Medical Association, Litjen Tan, Ph.D., Chicago, Illinois; American Pharmaceutical Association, Stephan L. Foster, Pharm.D., Memphis, Tennessee; Association of Teachers of Preventive Medicine, W. Paul McKinney, M.D., Louisville, Kentucky; Canadian National Advisory Committee on Immunization, Victor Marchessault, M.D., Cumberland, Ontario, Canada; Healthcare Infection Control Practices Advisory Committee, Jane D. Siegel, M.D., Dallas, Texas; Infectious Diseases Society of America, Samuel L. Katz, M.D., Durham, North Carolina, and William Schaffner, M.D., Nashville, Tennessee; London Department of Health, David M. Salisbury, M.D., London, United Kingdom; National Association of County and City Health Officials, J. Henry Hershey, M.D., Christiansburg, Virginia; National Coalition for Adult Immunization, David A. Neumann, Ph.D., Bethesda, Maryland; National Immunization Council and Child Health Program, Mexico, Jose Ignacio Santos, M.D., Mexico City, Mexico; National Medical Association, Rudolph E. Jackson, M.D., Atlanta, Georgia; National Vaccine Advisory Committee, Georges Peter, M.D., Providence, Rhode Island; and Pharmaceutical Research and Manufacturers of America, Geno Germano, St. Davids, Pennsylvania.

### **ACIP Influenza Working Group**

**Chair:** Bonnie M. Word, M.D., Monmouth Junction, New Jersey.

**Members:** T. Randolph Graydon, Kristin Lee Nichol, M.D., Margaret B. Rennels, M.D., and Richard Zimmerman, M.D., ACIP; Jon Abramson, M.D., American Academy of Pediatrics; Eric K. France, M.D., American Association of Health Plans; Stanley A. Gall, M.D., American College of Obstetricians and Gynecologists; Linda C. Lambert, Ph.D., National Institutes of Health; Roland A. Levandowski, M.D., and ChrisAnna M. Mink, M.D., Food and Drug Administration; Kathleen M. Neuzil, M.D., American College of Physicians; Fred Ruben, M.D., Pharmaceutical Research and Manufacturers of America; William Schaffner, M.D., Infectious Diseases Society of America; Susan Lett, M.D., Massachusetts Department of Health; Richard D. Clover, M.D., and Martin Mahoney, M.D., Ph.D., American Academy of Family Physicians; and Nancy J. Cox, Ph.D., Keiji Fukuda, M.D., James A. Singleton, M.S., Marika Iwane, Ph.D., Gina T. Mootrey, D.O., Dennis J. O'Mara, and William W. Thompson, Ph.D., Centers for Disease Control and Prevention.

All *MMWR* references are available on the Internet at <http://www.cdc.gov/mmwr>. Use the search function to find specific articles.

Use of trade names and commercial sources is for identification only and does not imply endorsement by the U.S. Department of Health and Human Services.

References to non-CDC sites on the Internet are provided as a service to *MMWR* readers and do not constitute or imply endorsement of these organizations or their programs by CDC or the U.S. Department of Health and Human Services. CDC is not responsible for the content of these sites. URL addresses listed in *MMWR* were current as of the date of publication.

The *Morbidity and Mortality Weekly Report (MMWR)* series is prepared by the Centers for Disease Control and Prevention (CDC) and is available free of charge in electronic format and on a paid subscription basis for paper copy. To receive an electronic copy each week, send an e-mail message to [listserv@listserv.cdc.gov](mailto:listserv@listserv.cdc.gov). The body content should read *SUBscribe mmwr-toc*. Electronic copy also is available from CDC's Internet server at <http://www.cdc.gov/mmwr> or from CDC's file transfer protocol server at <ftp://ftp.cdc.gov/pub/publications/mmwr>. To subscribe for paper copy, contact Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402; telephone 202-512-1800.

Data in the weekly *MMWR* are provisional, based on weekly reports to CDC by state health departments. The reporting week concludes at close of business on Friday; compiled data on a national basis are officially released to the public on the following Friday. Address inquiries about the *MMWR* series, including material to be considered for publication, to Editor, *MMWR* Series, Mailstop C-08, CDC, 1600 Clifton Rd., N.E., Atlanta, GA 30333; telephone 888-232-3228.

All material in the *MMWR* series is in the public domain and may be used and reprinted without permission; however, citation of the source is appreciated.