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***Inside:* Continuing Education Examination**

Prevention and Control of Influenza

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Prevention and Control of Influenza

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Summary

*This report updates the 2000 recommendations by the Advisory Committee on Immunization Practices (ACIP) on the use of influenza vaccine and antiviral agents (*MMWR *2000;49[No. RR-3]:1–38). The 2001 recommendations include new or updated information regarding a) the cost-effectiveness of influenza vaccination; b) the influenza vaccine supply; c) neuraminidase-inhibitor antiviral drugs; d) the 2001–2002 trivalent vaccine virus strains, which are A/Moscow/10/99 (H3N2)-like, A/New Caledonia/20/99 (H1N1)-like, and B/Sichuan/379/99-like strains; and e) extension of the optimal time period for vaccination through November. A link to this report and other information regarding influenza can be accessed at the website for the Influenza Branch, Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, CDC at <http://www.cdc.gov/ncidod/diseases/flu/fluvirus.htm>.*

INTRODUCTION

Epidemics of influenza typically occur during the winter months and are responsible for an average of approximately 20,000 deaths per year in the United States (*1,2*). 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 (*3–5*). Rates of infection are highest among children, but rates of serious illness and death are highest among persons aged ≥65 years and persons of any age who have medical conditions that place them at increased risk for complications from influenza (*3,6–8*).

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 a) groups that are at increased risk for influenza-related complications (e.g., persons aged ≥65 years and persons of any age with certain chronic medical conditions); b) the group aged 50–64 years because this group has an elevated prevalence of certain chronic medical conditions; and c) persons who live with or care for persons at high risk (e.g., health-care workers and household members who have frequent contact with persons at high risk and can transmit influenza infections to these 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 (*9–18*). Although influenza vaccination levels have increased substantially, further improvements in vaccine coverage levels are needed, particularly among persons at high risk aged <65 years. The ACIP recommends the use of strategies to improve vaccination levels, including the use of reminder/recall systems and standing orders programs (*19,20*).

Although influenza vaccination remains the cornerstone for the control and treatment of influenza, updated information is also presented on antiviral medications because these agents are an adjunct to vaccine.

Primary Changes in the Recommendations

These recommendations include five principal changes:

- Information regarding the cost-effectiveness of influenza vaccination has been added.
- Information regarding the influenza vaccine supply has been added.
- Information regarding neuraminidase-inhibitor antiviral drugs has been updated.
- The 2001–2002 trivalent vaccine virus strains are A/Moscow/10/99 (H3N2)-like, A/New Caledonia/20/99 (H1N1)-like, and B/Sichuan/379/99-like strains.
- The recommended optimal time period for vaccinating individuals is October–November.

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. 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, especially 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 influenza virus type or subtype. 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 incorporation of one or more 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*). Persons can be infectious starting the day before symptoms begin through approximately 5 days after illness onset; children can be infectious for a longer period.

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) (*25*). 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 section). Reported sensitivity and specificity of clinical definitions for influenza-like illness that include fever and cough have ranged from 63% to 78% and 55% to 71%, respectively, compared with viral culture (*26,27*). 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 (*28*).

Influenza illness typically resolves after several days for most persons, although cough and malaise can persist for ≥2 weeks. In some 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 co-infection with other viral or bacterial pathogens (*29*). Influenza infection has also been associated with encephalopathy, transverse myelitis, Reye syndrome, myositis, myocarditis, and pericarditis (*29*).

Hospitalizations and Deaths from Influenza

The risks for complications, hospitalizations, and deaths from influenza are higher among persons aged ≥65 years, very young children, and persons of any age with certain underlying health conditions than among healthy older children and younger adults (*1,30–33*). 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 conditions to 100/100,000 population for those without high-risk conditions (*34,35*). Within the 0–4 age group, hospitalization rates are highest among children aged 0–1 years and are comparable to rates found among persons ≥65 years (*36,37*) (Table 1).

During influenza epidemics from 1969–1970 through 1994–1995, the estimated overall number of influenza-associated hospitalizations in the United States has 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 (*38*).

During influenza epidemics, influenza-related deaths can result from pneumonia as well as from exacerbations of cardiopulmonary conditions and other chronic diseases. In studies of influenza epidemics occurring from 1972–1973 through 1994–1995, excess deaths (i.e., the number of influenza-related deaths above a projected baseline of expected deaths) occurred during 19 of 23 influenza epidemics (*39*) (Influenza Branch, Division of Viral and Rickettsial Diseases [DVRD], National Center for Infectious Diseases [NCID], CDC, unpublished data, 1998). During those 19 influenza seasons, estimated rates of influenza-associated deaths ranged from approximately 30 to >150 deaths/100,000 persons aged ≥65 years (Influenza Branch, DVRD, NCID, CDC, unpublished data, 1998). Older adults currently account for >90% of deaths attributed to

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 at high risk	Hospitalizations/ 100,000 persons not at high risk
1973–1993[†§]	Tennessee	0–11 mos	1,900	496–1,038[¶]
1973–1993[3§**]	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 would be expected to decrease as vaccination rates increased. Vaccination can be expected to reduce influenza-related hospitalizations by 30%–70% among elderly 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 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.

pneumonia and influenza (*40*). From 1972–1973 through 1994–1995, >20,000 influenza-associated deaths were estimated to occur during each of 11 different U.S. epidemics, and >40,000 influenza-associated deaths were estimated for each of 6 of these 11 epidemics (*39*) (Influenza Branch, DVRD, NCID, CDC, unpublished data, 1998). In the United States, pneumonia and influenza deaths might be increasing in part because the number of elderly persons is increasing (*41*).

Options for Controlling Influenza

In the United States, the main option for reducing the impact of influenza is immunoprophylaxis with inactivated (i.e., killed virus) vaccine (see Recommendations for the Use of Influenza Vaccine). Vaccinating persons at high risk for complications before the influenza season each year is the most effective means of reducing the impact 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) and among staff can reduce the risk for outbreaks by inducing herd immunity (*14*). Vaccination of health-care workers and other persons in close contact with persons in groups at high risk can also reduce transmission of influenza and subsequent influenza-related complications.

The use of influenza-specific antiviral drugs for chemoprophylaxis or treatment of influenza is an important adjunct to vaccine (see Recommendations for the Use of Antiviral Agents for Influenza). However, antiviral medications are not a substitute for vaccination.

Influenza Vaccine Composition

Influenza vaccine contains three strains (i.e., 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) (*42*). Subvirion and purified surface-antigen preparations are available. Because the vaccine viruses are initially grown in embryonated hens' eggs, the vaccine might contain small amounts of residual egg protein. Influenza vaccine distributed in the United States might also contain thimerosal, a mercury-containing compound, as the preservative (*43*). Manufacturing processes differ by manufacturer. Certain manufacturers might use additional compounds to inactivate the influenza viruses, and they might use an antibiotic to prevent bacterial contamination. Package inserts should be consulted for additional information.

The trivalent influenza vaccine prepared for the 2001–2002 season will include A/Moscow/10/99 (H3N2)-like, A/New Caledonia/20/99 (H1N1)-like, and B/Sichuan/379/99-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/Sichuan/379/99-like antigen, they will use one of the antigenically equivalent viruses B/Johannesburg/5/99, B/Victoria/504/2000, or B/Guangdong/120/2000. These viruses will be used because of their growth properties and because they are representative of currently circulating A (H3N2) and B 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. Most vaccinated children and young adults develop high postvaccination hemagglutination-inhibition antibody titers (*44,45*). These antibody titers are protective against illness caused by strains similar to those in the vaccine (*45–47*). When the vaccine and circulating viruses are antigenically similar, influenza vaccine prevents influenza illness in approximately 70%–90% of healthy persons aged <65 years (*48*). Vaccination of healthy adults also has resulted in decreased work absenteeism and decreased use of health-care resources, including the use of antibiotics, when the vaccine and circulating viruses are well-matched (*10–13,49,50*). Other studies suggest that the use of trivalent inactivated influenza vaccine decreases the incidence of influenza-associated otitis media and the use of antibiotics among children (*17,18*).

Elderly 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 (*51–53*). However, among such persons, the vaccine can be effective in preventing secondary complications and reducing the risk for influenza-related hospitalization and death (*14–16*). 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 (*16,54*). 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, even though the effectiveness in preventing influenza illness often ranges from 30% to 40% (*55,56*).

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 ≥65 years conducted in the United States have found overall societal cost-savings and substantial reductions in hospitalization and death (*16,54,57*). Studies of adults aged <65 years have shown that vaccination can reduce both direct medical costs and indirect costs from work absenteeism (*9,11–13,49*). Reductions of 34%–44% in physician visits, 32%–45% in lost work days (*11,13*), and 25% in antibiotic use have been reported (*13*). One cost-effectiveness meta-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 (*49*). Another cost-benefit economic model estimated an average annual savings of $13.66/person vaccinated (*58*). 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 (*9,59,60*). However, in a study that included all age groups, cost-utility improved with increasing age and among those with chronic medical conditions (*9*). Among persons aged ≥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 ≥65 years, influenza vaccination levels increased from 33% in 1989 (*61*) to 63% in 1997 and 1998 (*62*), surpassing the Healthy People 2000 goal of 60% (*63*). Although influenza vaccination coverage increased through 1997 among black, Hispanic, and white populations, vaccination levels among blacks and Hispanics continue to lag behind those among whites (*62,64*). In 1998, the influenza vaccination rate among persons aged ≥65 years were 66% among non-Hispanic whites, 46% among non-Hispanic blacks, and 50% among Hispanics (*62*).

Possible reasons for the increase in influenza vaccination levels among persons aged ≥65 years through 1997 include greater acceptance of preventive medical services by practitioners, increased delivery and administration of vaccine by health-care providers and sources other than physicians, new information regarding influenza vaccine effectiveness, cost-effectiveness, and safety, and the initiation of Medicare reimbursement for influenza vaccination in 1993 (*9,15,16,55,56,65,66*). Continued monitoring is needed to determine if vaccination coverage among persons aged ≥65 years has reached a peak or plateau. The Healthy People 2010 objective is to achieve vaccination coverage for 90% of persons aged ≥65 years (*67*).

In 1997 and 1998, vaccination rate estimates among nursing home residents were 64%–82% and 83%, respectively (*68,69*). 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% (*63,67*).

In 1998, the overall vaccination rate for adults aged 18–64 years with high-risk conditions was 31%, far short of the Healthy People 2000 goal of 60% (*62,63*). Among persons aged 50–64 years, 43% of those with chronic medical conditions and 29% of those without chronic medical conditions received influenza vaccine. Only 23% of adults younger than 50 years with high-risk conditions were vaccinated (National Immunization Program [NIP], CDC, unpublished data, 2000).

Reported vaccination rates of children at high risk are low. One study conducted among patients in health maintenance organizations found influenza vaccination rates ranging from 9% to 10% among asthmatic children (*70*), and a rate of 25% was found among children with severe-to-moderate asthma who attended an allergy and immunology clinic (*71*). 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, the National Health Interview Survey found vaccination rates of only 34% and 37% among health-care workers in the 1997 and 1998 surveys, respectively (*72*; NIP, CDC, unpublished data, 2001). Vaccination of health-care workers has been associated with reduced work absenteeism (*10*) and fewer deaths among nursing home patients (*73,74*).

Limited information is available regarding the use of influenza vaccine among pregnant women. Among women aged 18–44 years without diabetes responding to the 1999 Behavioral Risk Factor Surveillance Survey, those reporting they were pregnant were less likely to report influenza vaccination in the past 12 months (9.6%) than those not pregnant (15.7%). Vaccination coverage among pregnant women did not significantly change during 1997–1999, whereas coverage among nonpregnant women increased from 14.4% in 1997. Though not directly measuring influenza vaccination among women who were past the second trimester of pregnancy during influenza season, these data indicate low compliance with the ACIP recommendations for pregnant women (*75*). In a study of influenza vaccine acceptance by pregnant women, 71% offered the vaccine chose to be vaccinated (*76*). However, a 1999 survey of obstetricians and gynecologists determined that only 39% gave influenza vaccine to obstetric patients although 86% agree that pregnant women's risk for influenza-related morbidity and mortality increased in the last two trimesters (*77*).

RECOMMENDATIONS FOR THE USE OF INFLUENZA VACCINE

Influenza vaccine is strongly recommended for any person aged ≥6 months who — because of age or underlying medical condition — is at increased risk for complications of influenza. In addition, health-care workers and other individuals (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 ≥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 groups of persons who are at increased risk for complications from influenza:

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

Approximately 35 million persons in the United States are aged ≥65 years; an additional 10–13 million adults aged 50–64 years, 15–18 million adults aged 18–49 years, and 8 million children aged 6 months–17 years have ≥1 medical conditions that are associated with an increased risk of influenza-related complications (NIP, CDC, unpublished data, 2000).

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. Approximately 41 million persons in the United States are aged 50–64 years, and 10–13 million (24%–32%) have ≥1 high-risk medical conditions (NIP, CDC, unpublished data, 2000). Influenza vaccine has been recommended for this entire age group to raise the low vaccination rates among persons in this age group with high-risk conditions. Age-based strategies have been 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 (*10–13*). Further, 50 years is an age when other preventive services begin and when routine assessment of vaccination and other preventive services has been recommended (*78,79*).

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 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 workers is associated with decreased deaths among nursing home patients (*73,74*). Vaccination of health-care workers and others in close contact with persons at high risk, including household members, is recommended. The following groups should be vaccinated:

- physicians, nurses, and other personnel in both hospital and outpatient-care settings, including emergency response workers;
- 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 members (including children) of persons in groups at high risk.

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 the distribution of the 2000–2001 influenza vaccine (*80*). In October 2000, ACIP recommended that persons at highest risk of influenza-related complications (i.e., persons aged $\geq$65 years and those aged <65 years with high-risk medical conditions) and health-care workers receive vaccine first. ACIP also recommended that special efforts be made to vaccinate all persons aged 50–64 years, beginning in December, and to continue efforts to vaccinate groups at high risk through December and later (*81*). The possibility of future influenza vaccine delivery delays or vaccine shortages remains. Steps to address such situations include identification and implementation of ways to strengthen the influenza vaccine supply, to improve targeted delivery of vaccine to groups at high risk, and to further encourage the administration of vaccine throughout the influenza season.

Additional Information Regarding Vaccination of Specific Populations

Pregnant Women

Influenza-associated excess deaths among pregnant women were documented during the pandemics of 1918–1919 and 1957–1958 (*82–85*). Case reports and limited studies also suggest that pregnancy can increase the risk for serious medical complications of influenza as a result of increases in heart rate, stroke volume, and oxygen consumption; decreases in lung capacity; and changes in immunologic function (*86–89*). 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 (*90*). 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. Using data from this study, researchers estimated that an average of 1–2 hospitalizations could be prevented for every 1,000 pregnant women vaccinated. Women who will be beyond the first trimester of pregnancy (>14 weeks' gestation) during the influenza season should be vaccinated. 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.

Because currently available influenza vaccine is an inactivated vaccine, experts consider influenza vaccination safe during any stage of pregnancy. A study of influenza vaccination of >2,000 pregnant women demonstrated no adverse fetal effects associated with influenza vaccine (*91*). However, additional data are needed to confirm the safety of vaccination during pregnancy. Some experts 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.

Influenza vaccine distributed in the United States contains thimerosal, a mercury-containing compound, as a preservative. This preservative 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 outweighs the potential risks for thimerosal (*92,93*).

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 (*94,95*). However, a retrospective study of young and middle-aged women enrolled in Tennessee's Medicaid program found 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 (*96*). Another study estimated that the risk for influenza-related death was 9.4–14.6/10,000 persons with AIDS compared with rates of 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 (*97*). Other reports demonstrate that influenza symptoms might be prolonged and the risk for complications from influenza increased for certain HIV-infected persons (*98,99*).

Influenza vaccination has been shown to produce substantial antibody titers against influenza in vaccinated HIV-infected persons who have minimal acquired immunodeficiency syndrome-related symptoms and high CD4+ T-lymphocyte cell counts (*100–103*). A small, randomized, placebo-controlled trial found that influenza vaccine was highly effective in preventing symptomatic, laboratory-confirmed influenza infection among HIV-infected persons with a mean of 400 CD4+ T-lymphocyte cells/mm^3; a limited number of persons with CD4+ T-lymphocyte cell counts of <200 were included in that study (*95*). Among patients who have advanced HIV disease and low CD4+ T-lymphocyte cell counts, influenza vaccine might not induce protective antibody titers (*102,103*); a second dose of vaccine does not improve the immune response in these persons (*103,104*).

One study found that HIV RNA levels increased transiently in one HIV-infected patient after influenza infection (*105*). 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 (*102,106*). Other studies using similar laboratory techniques have not documented a substantial increase in the replication of HIV (*107–109*). Deterioration of CD4+ T-lymphocyte cell counts or progression of HIV disease have not been demonstrated among HIV-infected persons after influenza vaccination compared with unvaccinated persons (*103,110*). Limited information is available concerning the effect of antiretroviral therapy on increases in HIV RNA levels after either natural influenza infection or influenza vaccination (*94,111*). 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 patients, 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 that include persons from areas of the world where influenza viruses are circulating. 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 large 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 ≥50 years and others at high risk might wish 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.

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 as young as age 6 months), depending on vaccine availability (see 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

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 of influenza can benefit from vaccine after appropriate allergy evaluation and desensitization. Information regarding vaccine components can be found 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

The optimal time to vaccinate persons in groups at high risk is usually during October–November. However, to avoid missed opportunities for vaccination, influenza vaccine should be offered to persons at high risk when they are seen by health-care providers for routine care or are hospitalized in September, provided that vaccine is available. In addition, health-care providers should also continue to offer vaccine to unvaccinated persons after November and throughout the influenza season 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 has not reached peak levels in the majority of recent seasons until late December through early March (Table 2) (*81,112*). Therefore, although the timing of influenza activity can vary by region, vaccine administered after November is likely to be beneficial in most influenza seasons. Adults develop peak antibody protection against influenza infection 2 weeks after vaccination (*113,114*).

Persons planning substantial organized vaccination campaigns might consider scheduling these events after mid-October. Although influenza vaccine generally becomes available by September, 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. In facilities housing elderly persons (e.g., nursing homes), vaccination before October generally should be avoided because antibody levels in such individuals can begin to decline within a few months after vaccination (*115,116*). (For information regarding vaccination of travelers, see Travelers.)

Dosage

Dosage recommendations vary according to age group (Table 3). Among previously unvaccinated children aged <9 years, two doses administered ≥1 months apart are recommended for satisfactory antibody responses. If possible, the second dose should be administered before December. Among adults, studies have indicated little or no improvement in antibody response when a second dose is administered during the same season (*117–120*). Even when the current influenza vaccine contains one or more of the antigens administered in previous years, annual vaccination with the current vaccine is necessary because immunity declines during the year following vaccination (*115,116*).

TABLE 2. Month of peak influenza activity during 19 influenza seasons — United States, 1982–2000

Month	December	January	February	March
Number (%) of years with peak influenza activity	4 (21%)	5 (26%)	7 (37%)	3 (16%)

TABLE 3. Influenza vaccine* dosage, by age group — United States, 2001–2002 season

Age group	Product†	Dose	Number of doses	Route§
6–35 mos	Split virus only	0.25 mL	1 or 2¶	Intramuscular
3–8 yrs	Split virus only	0.50 mL	1 or 2¶	Intramuscular
9–12 yrs	Split virus only	0.50 mL	1	Intramuscular
>12 yrs	Whole or split virus**	0.50 mL	1	Intramuscular

* Contains 15 mg each of A/New Caledonia/20/99 (H1N1)-like, A/Moscow/10/99 (H3N2)-like, and B/Sichuan/379/99-like strains. For the A/Moscow/10/99 (H3N2)-like antigen, manufacturers will use the antigenically equivalent A/Panama/2007/99 (H3N2) virus. For the B/Sichuan/379/99-like antigen, manufacturers will use one of the antigenically equivalent viruses B/Johannesburg/5/99, B/Victoria/504/2000, or B/Guangdong/120/2000. Manufacturers include Aventis Pasteur, Inc. (Fluzone® split); Evans Vaccines, Ltd. (Fluvirin® purified surface antigen vaccine); and Wyeth Lederle Laboratories (Flushield™ split). For further product information call Aventis Pasteur, (800) 822-2463; Evans Vaccines, (800) 200-4278; or Wyeth Lederle, (800) 358-7443.

† Because of their decreased potential for causing febrile reactions, only split-virus vaccines should be used for children. The vaccines 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.

§ 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 ≥1 months apart are recommended for children aged <9 years who are receiving influenza vaccine for the first time.

** No whole virus vaccine will be distributed in the U.S. during the 2001–2002 influenza season.

Vaccine prepared for a previous influenza season should not be administered to provide protection for the current season.

Use of Inactivated Influenza Vaccine Among Children

Of the three influenza vaccines currently licensed in the United States, two influenza vaccines (Flushield™, from Wyeth Laboratories, Inc., and Fluzone® split, from Aventis Pasteur, Inc.) are approved for use among persons aged ≥6 months. One other influenza vaccine, Fluvirin® (Evans Vaccines Ltd.), is labeled in the United States for use only among persons aged ≥4 years because its efficacy among younger persons has not been demonstrated. Providers should use influenza vaccine that has been approved for vaccinating children aged 6 months–3 years.

Route

The intramuscular route is recommended for influenza vaccine. Adults and older children should be vaccinated in the deltoid muscle. A needle length ≥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 (*121*). Infants and young children should be vaccinated in the anterolateral aspect of the thigh (*122*).

Side Effects and Adverse Reactions

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

Local Reactions

In placebo-controlled blinded studies, the most frequent side effect of vaccination is soreness at the vaccination site (affecting 10%–64% of patients) that lasts ≤2 days (*123–125*). These local reactions generally are mild and rarely interfere with the person's ability to conduct usual daily activities.

Systemic Reactions

Fever, malaise, myalgia, and other systemic symptoms can occur following vaccination and most often affect persons who have had no prior exposure to the influenza virus antigens in the vaccine (e.g., young children) (*126,127*). These reactions begin 6–12 hours after vaccination and can persist for 1–2 days.

Recent placebo-controlled trials demonstrate that among elderly 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 (*123,125*).

Immediate — presumably allergic — reactions (e.g., hives, angioedema, allergic asthma, and systemic anaphylaxis) rarely occur after influenza vaccination (*128*). These reactions probably result from hypersensitivity to some vaccine component; most reactions likely are caused by residual egg protein. Although current influenza vaccines contain only a small quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Persons who have developed hives, have had swelling of the lips or tongue, or 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 (*129,130*).

Hypersensitivity reactions to any vaccine component can occur. Although exposure to vaccines containing thimerosal can lead to induction of hypersensitivity, most patients do not develop reactions to thimerosal when it is administered as a component of vaccines, even when patch or intradermal tests for thimerosal indicate hypersensitivity (*131,132*). When reported, hypersensitivity to thimerosal usually has consisted of local, delayed-type hypersensitivity reactions (*131*).

Guillain-Barré Syndrome

The 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré syndrome (GBS) (*133,134*). Among persons who received the swine influenza vaccine in 1976, the rate of GBS that exceeded the background rate was <10 cases/1,000,000 persons vaccinated. Evidence for a causal relationship of GBS with subsequent vaccines prepared from other influenza viruses is unclear. Obtaining strong epidemiologic evidence for a possible small increase in risk is difficult for such a rare condition as GBS, which has an annual incidence of 10–20 cases/1,000,000 adults (*135*), and stretches the limits of epidemiologic investigation. More definitive data probably will require the use of 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 (*136–138*). However, in a study of the 1992–1993 and 1993–1994 seasons, the overall relative risk for GBS was 1.7 (95% confidence interval = 1.0–2.8; $p = 0.04$) during the 6 weeks after vaccination, representing approximately 1 additional case of GBS/1,000,000 persons vaccinated. The combined number of GBS cases peaked 2 weeks after vaccination (*139*). 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 per million persons vaccinated. Cases of GBS after influenza infection have been reported, but no epidemiologic studies have documented such an association (*140,141*). Substantial evidence exists that several infectious illnesses, most notably *Campylobacter jejuni*, as well as upper-respiratory tract infections in general are associated with GBS (*135,142–144*).

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/1,000,000 persons vaccinated is substantially less than the risk for severe influenza, which could be prevented by vaccination among all age groups, especially persons aged ≥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 greatly outweigh the possible risks for developing vaccine-associated GBS. The average case-fatality ratio for GBS is 6% and increases with age (*135,145*). 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 developing GBS than persons without such a history (*136,146*). Thus, the likelihood of coincidentally developing 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 not known; therefore, avoiding vaccinating persons who are not at high risk for severe influenza complications and who are known to have developed GBS within 6 weeks after a previous influenza vaccination is prudent. As an alternative, physicians might consider the use of influenza antiviral chemoprophylaxis for these persons. Although data are limited, for most 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

The target groups for influenza and pneumococcal vaccination overlap considerably (*147*). For persons at high risk who have not previously been vaccinated with pneumococcal vaccine, health-care providers should strongly consider administering pneumococcal and influenza vaccines concurrently. Both vaccines can be administered at the same time at different sites without increasing side effects (*148,149*). 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 (*147*). Children at high risk for influenza-related complications 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 (*19*). Use of standing orders programs is recommended for long-term care facilities (e.g., nursing homes and skilled nursing facilities) under the supervision of a medical director to ensure the administration of recommended vaccinations for adults. Other settings (e.g., inpatient and outpatient facilities, managed care organizations, assisted living facilities, correctional facilities, pharmacies, adult workplaces, and home health-care agencies) 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 or telephone of the need for vaccination.

Outpatient Facilities Providing Episodic or Acute Care

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

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 anytime afterwards. All residents should be vaccinated at one time, preceding the influenza season. Residents admitted during the winter months after completion of the 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 ≥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 (*150*). Thus, the hospital serves as a setting in which persons at increased risk for subsequent hospitalization can be identified and vaccinated. Use of standing orders in this setting has been successful in increasing vaccination of hospitalized persons (*151*).

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

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 ≥50 Years

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

Health-Care Workers

Before the influenza season, 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 workers 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 workers convenient access to influenza vaccine at the work site, free of charge, as part of employee health programs.

Evolving Developments Related to Influenza Vaccine

Potential New Vaccines

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 (*152–156*). The viruses in these vaccines replicate in the upper respiratory tract and elicit a specific protective immune response. LAIVs have been studied as monovalent, bivalent, and trivalent formulations (*155,156*). LAIVs consist of live viruses that induce minimal symptoms (i.e., attenuated) and that replicate poorly at temperatures found in the lower respiratory tract (i.e., temperature-sensitive). Possible advantages of LAIVs are their potential to induce a broad mucosal and systemic immune response, ease of administration, and the acceptability of an intranasal route of administration compared with injectable vaccines. 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 found to be approximately equivalent in terms of effectiveness (*157*). In a recent 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 otitis media among vaccinated children by 30%, and reduced otitis media with concomitant antibiotic use by 35% compared with unvaccinated children (*158*). In a follow-up study during the 1997–1998 season, the trivalent LAIV was 86% effective in preventing culture-positive influenza among children, despite a poor match between the vaccine's influenza A (H3N2) component and the predominant circulating influenza A (H3N2) virus (*159*). A study conducted among healthy adults during the same season found a 9%–24% reduction in febrile respiratory illnesses and 13%–28% reduction in lost work days (*160*). No study has directly compared the efficacy or effectiveness of trivalent inactivated vaccine and trivalent LAIV.

Potential Addition of Young Children to Groups Recommended for Vaccination

During 1998, the ACIP formed a working group to explore issues related to the potential expansion of recommendations for the use of influenza vaccine. The ACIP influenza working group is considering the impact of influenza among young children as well as the potential safety issues and logistic and economic consequences of recommending routine vaccination of young healthy children.

Studies indicate that rates of hospitalization are higher among young children than older children when influenza viruses are in circulation (*34,36,37,161,162*). The increased rates of hospitalization are comparable with rates for other groups at high risk.

However, the interpretation of these findings has been confounded by cocirculation 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 (*163–165*). Recent studies have attempted to separate the effects of respiratory syncytial viruses and influenza viruses on rates of hospitalization among children aged <5 years who do not have high-risk conditions (*36,37*). Both studies indicate 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).

Because very young healthy children are at increased risk for influenza-related hospitalization, the ACIP is studying the benefits, risks, economic consequences and logistical issues associated with routine immunization of this age group. Meanwhile, ACIP continues to support vaccination of healthy children aged ≥6 months whose parents wish to decrease their child's risk for influenza infection, in addition to vaccinating children with high-risk medical conditions.

RECOMMENDATIONS FOR THE USE OF ANTIVIRAL AGENTS FOR INFLUENZA

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

Amantadine and rimantadine are chemically related antiviral drugs with activity against influenza A viruses but not influenza B viruses. Amantadine was approved in 1966 for prophylaxis of influenza A (H2N2) infection and was later approved in 1976 for the treatment and prophylaxis of influenza type A virus infections among adults and children aged ≥1 years. Rimantadine was approved in 1993 for treatment and prophylaxis of infection among adults and prophylaxis among children. Although rimantadine is approved only for prophylaxis of infection among children, certain experts in the management of influenza consider it appropriate for treatment among children (see American Academy of Pediatrics, 2000 Red Book, in Additional Information Regarding Influenza Infection Control Among Specific Populations).

Zanamivir and oseltamivir are neuraminidase inhibitors with activity against both influenza A and B viruses. Both zanamivir and oseltamivir were approved in 1999 for the treatment of uncomplicated influenza infections. Zanamivir is approved for treatment for persons aged ≥7 years, and oseltamivir is approved for treatment for persons aged ≥1 years. In 2000, oseltamivir was approved for prophylaxis of persons aged ≥13 years.

The four drugs differ in terms of their pharmacokinetics, side effects, 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 Food and Drug Administration 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. 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, and immunofluorescence (*24*). Sensitivity and specificity of any test for influenza might vary by the laboratory that performs the test and by the type of test used. As with any diagnostic test, results should be evaluated in the context of other clinical information available to the physician.

Several commercial rapid diagnostic tests are available that can be used by laboratories in outpatient settings to detect influenza viruses within 30 minutes (*24,166*). These rapid tests differ in the types of influenza virus they can detect and whether or not they can distinguish between influenza types. Different tests can detect a) only influenza A viruses; b) both influenza A and B viruses but not distinguish between the two types, or c) both influenza A and B and distinguish between the two. Sensitivity and specificity of rapid tests are lower than for viral culture and vary by test. In addition, the types of specimens acceptable for use (i.e., throat swab, nasal wash, or nasal swab) also vary. Package inserts and the laboratory performing the test should be consulted for more details.

Despite the availability of rapid diagnostic tests, the collection of 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 prophylaxis, 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 (*49,167–180*). More clinical data are available concerning the effectiveness of zanamivir and oseltamivir for treatment of influenza A infection than for treatment of influenza B infection (*169,174–179,181–184*). However, in vitro data (*185–190*), studies of treatment among mice and ferrets (*186,187,191,192*), and clinical studies have documented that zanamivir and oseltamivir have activity against influenza B viruses (*173,177–179,183,184*).

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 (*193*). 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 (*167,169,170,172,173,180,194–197*). Fewer studies of the efficacy of influenza antivirals have been conducted among pediatric populations compared with adults (*167,170,176,177,196,198,199*). One study of oseltamivir treatment documented a decreased incidence of otitis media among children (*177*).

To reduce the emergence of antiviral drug-resistant viruses, amantadine or rimantadine therapy for persons with influenza-like illness should be discontinued as soon as clinically warranted, generally 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.

Prophylaxis

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 prophylaxis of influenza A infection, but are not effective against influenza B. Both drugs are approximately 70%–90% effective in preventing illness from influenza A infection (*49,167,196*). When used as prophylaxis, these antiviral agents can prevent illness while permitting subclinical infection and the 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 (*167*). 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 (*167,195,200–202*).

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%) (*203,204*). Both antiviral agents have also been reported to prevent influenza illness among persons given chemoprophylaxis after a household member was diagnosed with influenza (*183,205*). Experience with prophylactic use of these agents in institutional settings or among patients with chronic medical conditions is limited (*179,206–211*). One 6-week study of oseltamivir prophylaxis among nursing home residents found a 92% reduction in influenza illness (*179,212*). Use of zanamivir has not been reported to impair the immunologic response to influenza vaccine (*178,213*). Data are not available on the efficacy of any of the four antiviral agents in preventing influenza among severely immune compromised 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 (*214*).

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 can take as long as 2 weeks (*118,119*). When influenza vaccine is given while influenza viruses are circulating, chemoprophylaxis should be considered for persons at high risk during the time from vaccination until immunity has developed. Children who receive influenza vaccine for the first time can require as long as 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 Deficiency. 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, especially 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

The use of antiviral drugs for treatment and prophylaxis of influenza is an important component of institutional outbreak control. In addition to the use of 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 (*215–217*). (For additional information regarding outbreak control in specific settings, refer to additional references in Additional Information Regarding Influenza Infection Control Among Specific Populations.)

Most published reports on the use of antiviral agents to control institutional influenza outbreaks are based on studies of influenza A outbreaks among nursing home populations where amantadine or rimantadine were used (*167,195,200–202*). Less information is available concerning the use of oseltamivir in influenza A or B institutional outbreaks (*210,212*). 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 is extremely useful.

When institutional outbreaks occur, chemoprophylaxis should be administered to all residents — regardless of whether they received influenza vaccinations during the previous fall — and should continue for ≥2 weeks or 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 (*218*).

To limit the potential transmission of drug-resistant virus during institutional outbreaks, 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 anti-viral 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. The use of amantadine among children aged <1 year has not been adequately evaluated. The Food and Drug Administration-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 (*219*).

Rimantadine. Rimantadine is approved for prophylaxis among children aged ≥1 years and for treatment in children aged ≥13 years. Although rimantadine is approved only for prophylaxis of infection among children, certain experts in the management of influenza consider it appropriate for treatment among children (see American Academy of Pediatrics, 2000 Red Book, in Additional Information Regarding Influenza Infection Control Among Specific Populations). The use of rimantadine among children aged <1 year has not been adequately evaluated. Rimantadine should be administered in one or two 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 (*220*).

Zanamivir. Zanamivir is not approved for use among children aged <7 years. The recommended dosage of zanamivir for treatment of influenza among persons aged ≥7 years is two inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) twice daily (approximately 12 hours apart) (*178*).

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

Antiviral agent	Age Groups				
	1–6 yrs	**7–9 yrs**	**10–12 yrs**	**13–64 yrs**	**≥65 yrs**
Amantadine*					
Treatment	5mg/kg/day up to 150 mg in two divided doses[†]	5mg/kg/day up to 150 mg in two divided doses[†]	100 mg twice daily[§]	100 mg twice daily[§]	≤100 mg/day
Prophylaxis	5mg/kg/day up to 150 mg in two divided doses[†]	5mg/kg/day up to 150 mg in two divided doses[†]	100 mg twice daily[§]	100 mg twice daily[§]	≤100 mg/day
Rimantadine[¶]					
Treatment**	NA[††]	NA	NA	100 mg twice daily[§]	100 or 200[§§] mg/day
Prophylaxis	5mg/kg/day up to 150 mg in two divided doses[†]	5mg/kg/day up to 150 mg in two divided doses[†]	100 mg twice daily[§]	100 mg twice daily[§]	100 or 200[§§] mg/day
Zanamivir[¶¶] * **					
Treatment	NA	10 mg twice daily	10 mg twice daily	10 mg twice daily	10 mg twice daily
Oseltamivir					
Treatment[†††]	Dose varies by child's weight[§§§]	Dose varies by child's weight[§§§]	Dose varies by child's weight[§§§]	75 mg twice daily	75 mg twice daily
Prophylaxis	NA	NA	NA	75 mg/day	75 mg/day

NOTE: Amantadine manufacturers include Endo Pharmaceuticals (Symmetrel,® tablet and syrup); Geneva Pharmaceuticals and Rosemont (Amantadine HCL, capsule); and Alpharma, Copley Pharmaceutical, HiTech Pharma, Mikart, Morton Grove, and Pharmaceutical Associates (Amantadine HCL, syrup). Rimantadine is manufactured by Forest Laboratories (Flumadine,® tablet and syrup). Zanamivir is manufactured by Glaxo Wellcome (Relenza,® inhaled powder). Oseltamivir is manufactured by Hoffman-LaRoche, Inc. (Tamiflu,® tablet and suspension).

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

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

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

¶ 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.

** Only approved for treatment among adults.

†† Not applicable.

§§ Elderly residents of nursing-homes 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 side effects when taking 200 mg/day.

¶¶ Zanamivir is administered via inhalation by using a plastic device included in the package with the medication. Patients will benefit from instruction and demonstration of correct use of the device.

*** Zanamivir is not approved for prophylaxis.

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

§§§ The dose recommendation for children who weigh <15 kg is 30 mg twice a day; for children weighing >15–23 kg, the dose is 45 mg twice a day; for children weighting >23–40 kg, the dose is 60 mg twice a day; and for children weighing >40 kg, the dose is 75 mg twice a day.

Oseltamivir. Oseltamivir is not approved for use among persons aged <1 year. Recommended treatment doses for children vary by the weight of the child: the dose recommendation for children who weigh ≤15 kg is 30 mg twice a day; for children weighing >15–23 kg, the dose is 45 mg twice a day; for those weighing >23–40 kg, the dose is 60 mg twice a day; and for children weighing >40 kg, the dose is 75 mg twice a day. The treatment dosage for persons ≥13 years is 75 mg twice daily. For children ≥13 years, the recommended dose for prophylaxis is 75 mg once a day (*179*).

Persons Aged ≥65 Years

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

Rimantadine. Among elderly 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 (*221*). However, chronically ill elderly persons have had a higher incidence of CNS and gastrointestinal symptoms and serum concentrations two to four times higher than among healthy, younger persons when rimantadine has been administered at a dosage of 200 mg/day (*167*).

For elderly nursing home residents, the dosage of rimantadine should be reduced to 100 mg/day for prophylaxis or treatment. For other elderly persons, further studies are needed to determine the optimal dosage. However, a reduction in dosage to 100 mg/day should be considered for all persons aged ≥65 years who experience side effects when taking a dosage of 200 mg/day.

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 ≤50 mL/min/1.73m^2. Guidelines for amantadine dosage on the basis of creatinine clearance are found 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 (*222*).

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 elderly 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 (*223*).

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 (*178,224*). However, a small number of healthy volunteers who were administered high doses of intravenous zanamivir tolerated systemic levels of zanamivir that were much higher than those resulting from administration of zanamivir by oral inhalation at the recommended dose (*225,226*). 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 (*178*).

Oseltamivir. Serum concentrations of oseltamivir carboxylate (GS4071), the active metabolite of oseltamivir, increase with declining renal function (*182,179*). For patients with creatinine clearance of 10–30 mL/min (*179*), a reduction of the treatment dose of oseltamivir to 75 mg once daily and in the prophylaxis dose 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 relationship between the drug and such changes has not been established (*227*).

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 (*228*). 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 (*229*). 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 (*178,179*). 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 (*178*).

Pharmacokinetics

Amantadine

Approximately 90% of amantadine is excreted unchanged in the urine by glomerular filtration and tubular secretion (*200,230–233*). 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 (*196*). The safety and pharmacokinetics of rimantadine among persons with liver disease have been evaluated only after single-dose administration (*196,234*). In a study of persons with chronic liver disease (most with stabilized cirrhosis), no alterations in liver function were observed after a single dose (*175,217*). However, for persons with severe liver dysfunction, the apparent clearance of rimantadine was 50% lower than that reported for persons without liver disease (*220*).

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 (*196,223*). 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 (*223*). 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 (*220,235*).

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 (*236,237*). 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 (*178,226*).

Oseltamivir

Approximately 80% of orally administered oseltamivir is absorbed systemically (*182*). 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 (*179,238*). Unmetabolized oseltamivir also is excreted in the urine by glomerular filtration and tubular secretion (*238*).

Side Effects and Adverse Reactions

When considering the use of influenza antiviral medications (i.e., choice of antiviral drug, dose, 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, difficulty concentrating, and lightheadedness) is higher among persons taking amantadine than among those taking rimantadine (*239*). In a 6-week study of prophylaxis among healthy adults, approximately 6% of participants taking rimantadine at a dosage of 200 mg/day experienced ≥1 CNS symptoms, compared with approximately 13% of those taking the same dosage of amantadine and 4% of those taking placebo (*239*). A study of elderly persons also demonstrated fewer CNS side effects associated with rimantadine compared with amantadine (*221*). 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 (*239*).

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) (*228*). 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 elderly persons who have been taking amantadine as prophylaxis at a dosage of 200 mg/day (*200*). 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 (*219*). Because rimantadine has been marketed for a shorter period than amantadine, its safety among certain patient populations (e.g. chronically ill and elderly persons) has been evaluated less frequently.

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 the use of a β_2-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 (FEV1) after treatment (*178,180*). 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 following administration of zanamivir (*178*). In addition, during postmarketing surveillance, cases of respiratory function deterioration following 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 in this population, zanamivir is generally not recommended for treatment for patients with underlying airway disease (*178*). 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 proper monitoring and supportive care, including the availability of short-acting bronchodilators (*193*). Patients with asthma or chronic obstructive pulmonary disease who use zanamivir are advised to a) have a fast-acting inhaled bronchodilator available when inhaling zanamivir and b) stop using zanamivir and contact their physician if they develop difficulty breathing (*178*). No clear 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 (*193*).

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) (*168–173,178,236*). 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 (*150,151,153,154,191*). Each of these symptoms was reported by <5% of persons in the clinical treatment studies combined (*178*).

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%) (*174,175,179,240*). 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 (*177*), whereas a limited number of adults enrolled in clinical treatment trials of oseltamivir discontinued treatment because of these symptoms (*179*). Similar types and rates of adverse events were found in studies of oseltamivir prophylaxis (*179*). Nausea and vomiting might be less severe if oseltamivir is taken with food (*179,240*).

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 (*89,241*). However, both amantadine and rimantadine have been demonstrated in animal studies to be teratogenic and embryotoxic when administered at very high doses (*219,220*). 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 package inserts [*178,179,219,220*]).

Drug Interactions

Careful observation is advised when amantadine is administered concurrently with drugs that affect CNS, especially CNS stimulants. Concomitant administration of antihistamines or anticholinergic drugs can increase the incidence of adverse CNS reactions (*167*). No clinically significant 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 important drug interactions have been predicted on the basis of in vitro data and data from studies of rats (*178,242*).

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 (*179,238*).

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 (*243*). Drug-resistant viruses can appear in approximately one third of patients when either amantadine or rimantadine is used for therapy (*199,244*). During the course of amantadine or rimantadine therapy, resistant influenza strains can replace sensitive strains within 2–3 days of starting therapy (*244,245*). 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 (*246,247*); however, the frequency with which resistant viruses are transmitted and their impact on efforts to control influenza are unknown. Amantadine- and rimantadine-resistant viruses are not more virulent or transmissible than sensitive viruses (*248*). The screening of epidemic strains of influenza A has rarely detected amantadine- and rimantadine-resistant viruses (*244,249,250*).

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, especially after 5–7 days of therapy (*199*). 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 (*251–258*), but induction of resistance requires several passages in cell culture. By contrast, resistance to amantadine and rimantadine in vitro can be induced with fewer passages in cell culture (*259,260*). Development of viral resistance to zanamivir and oseltamivir during treatment has been identified but does not appear to be frequent (*179,261–264*). In clinical treatment studies using oseltamivir, 1.3% of posttreatment isolates from patients aged ≥13 years and 8.6% among patients aged 1–12 years had decreased susceptibility to oseltamivir (*179*). No isolates with reduced susceptibility to zanamivir have been reported from clinical trials, although the number of post-treatment isolates tested is limited (*265*), and the risk for emergence of zanamivir resistant isolates cannot be quantified (*178*). Only one clinical isolate with reduced susceptibility to zanamivir, obtained from an immunocompromised child on prolonged therapy, has been reported (*262*). Currently available diagnostic tests are not optimal for detecting clinical resistance, and better tests as well as more testing are needed before firm conclusions can be reached (*265*). Postmarketing surveillance for neuraminidase inhibitor-resistant influenza viruses is being conducted.

SOURCES OF INFORMATION REGARDING INFLUENZA AND ITS SURVEILLANCE

Information regarding influenza surveillance is available through the CDC Voice Information System (influenza update) at (888) 232-3228; CDC Fax Information Service at (888) 232-3299; or website for the Influenza Branch, DVRD, NCID, CDC at <http://www.cdc.gov/ncidod/diseases/flu/weekly.htm>. During October–May, the information is updated at least every other week. In addition, periodic updates regarding influenza are published in the weekly *MMWR*. State and local health departments should be consulted regarding availability of influenza vaccine, access to vaccination programs, information regarding state or local influenza activity, and for reporting influenza outbreaks and receiving advice regarding outbreak control.

ADDITIONAL INFORMATION REGARDING INFLUENZA INFECTION CONTROL AMONG SPECIFIC POPULATIONS

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

- 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.
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- 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. J Am Med Directors Assoc 2000;1(Suppl):S2–37.
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- CDC. General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 1994;43(No. RR-1):1–38.
- 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.
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CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION
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MORBIDITY AND MORTALITY WEEKLY REPORT
April 20, 2001 / Vol. 50 / No. RR-4
Recommendations and Reports

Continuing Education Activity Sponsored by CDC

Prevention and Control of Influenza
Recommendations of the Advisory Committee on Immunization Practices (ACIP)

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INSTRUCTIONS

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1. Read this *MMWR* (Vol. 50, RR-4), which contains the correct answers to the questions beginning on the next page.
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GOAL AND OBJECTIVES

This *MMWR* provides recommendations regarding the prevention and control of influenza. These recommendations were developed by CDC staff and the Influenza Working Group of the Advisory Committee on Immunization Practices (ACIP). The goal of this report is to provide guidance for the use of influenza vaccine and influenza antiviral agents in the United States. Upon completion of this educational activity, the reader should be able to a) describe the disease burden of influenza in the United States; b) describe the characteristics of the currently licensed influenza vaccine; c) list the primary target groups for annual influenza vaccination; and d) recognize the most common adverse reactions following administration of influenza vaccine.

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

1. Which of the following statements is true concerning the burden of influenza in the United States?

A. Rates of influenza virus infection are highest among children.

B. On average, >100,000 influenza-related hospitalizations occur each year.

C. Older adults account for >90% of deaths from influenza.

D. Pneumonia and influenza deaths have increased in recent years.

E. All of the above statements are true concerning the burden of influenza in the United States.

2. What is the main option for reducing the impact of influenza in the United States?

A. Antibiotics.

B. Vitamin supplements.

C. Influenza vaccine.

D. Antiviral agents.

E. Improvement in indoor air quality.

3. Which of the following is true regarding influenza vaccine?

A. Influenza vaccine contains two strains of influenza virus.

B. Influenza vaccine viruses are grown in human diploid cell tissue culture.

C. Effectiveness of influenza vaccine is not influenced by the age of the recipient.

D. Influenza vaccine has been shown to be 70%–90% effective in preventing influenza among healthy persons aged <65 years.

E. All the above statements are true regarding influenza vaccine.

4. Which of the following best describes the currently licensed influenza vaccine?

A. Inactivated virus.

B. Live attenuated virus.

C. Toxoid.

D. Protein conjugate.

E. Cloned DNA.

5. Which of the following groups should receive two doses of influenza vaccine during the same season?

A. Persons with human immunodeficiency virus infection.

B. Elderly persons who reside in extended care facilities.

C. Unvaccinated children <9 years of age receiving influenza vaccine for the first time.

D. Health-care workers.

E. Adults aged ≥50 years.

6. Which of the following are among the primary target groups for annual influenza vaccination?

A. Children with asthma.

B. Persons aged ≥50 years.

C. Health-care providers.

D. Women who will be in the second or third trimester of pregnancy during influenza season.

E. All the above are among the primary target groups for annual influenza vaccination.

7. What is the most common adverse reaction following influenza vaccination?

A. Allergic reactions (e.g., angioedema).

B. Soreness at the injection site.

C. An illness identical to influenza.

D. Fever.

E. Guillain-Barré syndrome.

8. Which of the following conditions is a valid contraindication or precaution for the use of influenza vaccine?

A. Current administration of antibiotics.

B. Breastfeeding.

C. Severe allergy to a component of the vaccine.

D. Recent administration of antibody-containing blood product (e.g., whole blood or immunoglobulin).

E. All of the above are valid contraindications or precautions to the use of influenza vaccine.

9. Which of the following statements is true concerning antiviral agents for influenza?

A. Influenza antiviral agents are approved only for the treatment of influenza A infection.

B. Antiviral agents do not reduce the response to influenza vaccine.

C. All influenza antiviral agents are equally effective against influenza A and B viruses.

D. Treatment of influenza with antiviral agents requires a course of therapy of ≥14 days.

E. Antiviral agents have been shown to reduce the risk of serious influenza-related complications.

10. 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.

11. 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.

12. 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.

13. Each fall, to approximately how many patients do you administer influenza vaccine?

A. None.
B. 1–5.
C. 6–20.
D. 21–50.
E. 51–100.
F. >100.

14. How much time did you spend reading this report and completing the exam?

A. <1 hour.
B. 1–1.5 hours.
C. 1.5–2 hours.
D. >2 hours.

15. After reading this report, I am confident I can describe the disease burden of influenza in the United States.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

16. After reading this report, I am confident I can describe the characteristics of the currently licenced influenza vaccine.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

17. After reading this report, I am confident I can list the primary target groups for annual influenza vaccination.

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 recognize the most common adverse reactions following administration of influenza vaccine.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

19. 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.

20. The tables are useful.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

21. 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.

22. These recommendations will affect my practice.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

23. 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 1–9

1. E; 2. C; 3. D; 4. A; 5. C; 6. E; 7. B; 8. C; 9. B.

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Prevention and Control of Influenza Recommendations of the Advisory Committee on Immunization Practices (ACIP)

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5. [ ] A [ ] B [ ] C [ ] D [ ] E
6. [ ] A [ ] B [ ] C [ ] D [ ] E
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22. [ ] A [ ] B [ ] C [ ] D [ ] E
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Signature ***Date I Completed Exam***

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