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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 & HUMAN SERVICES
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Prevention and Control of Influenza

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Summary

*This report updates 1999 recommendations by the Advisory Committee on Immunization Practices (ACIP) on the use of influenza vaccine and antiviral agents (*MMWR *1999;48[No. RR-4]:1–29). These recommendations include five principal changes: a) the age for universal vaccination has been lowered to 50 years from 65 years; b) scheduling of large, organized vaccination campaigns after mid-October may be considered because the availability of vaccine in any location cannot be assured consistently in the early fall; c) 2000–2001 trivalent vaccine virus strains are A/Moscow/10/99 (H3N2)-like, A/New Caledonia/20/99 (H1N1)-like, and B/Beijing/184/93-like strains; d) information on neuraminidase-inhibitor antiviral drugs has been added; and e) a list of other influenza-related infection control documents for special populations has been added. This report and other information on 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 occur during the winter months nearly every year and are responsible for an average of approximately 20,000 deaths per year in the United States (*1,2*). Influenza viruses also can cause global epidemics of disease, known as pandemics, during which rates of illness and death from influenza-related complications can increase dramatically. Influenza viruses cause disease in 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 high risk for complications from influenza (*3,6–8*).

Influenza vaccine is the primary method for preventing influenza and its more severe complications. In this report from the Advisory Committee on Immunization Practices (ACIP), the primary target group for influenza vaccination includes persons who are at high risk for serious complications from influenza, including approximately 35 million persons aged ≥65 years and approximately 33–39 million persons aged <65 years who have chronic underlying medical conditions (National Immunization Program, CDC, unpublished data, 2000).

Beginning with the 2000–2001 influenza season, the ACIP has added persons aged 50–64 years to the primary target group for annual influenza vaccination. This age group was added because a substantial proportion of persons aged 50–64 years (24%–32%) have one or more chronic medical conditions that place them at high risk for influenza-related hospitalization and death. Rates of influenza-related excess hospitalization among adults aged <65 years with one or more high-risk conditions have been estimated at

56–635 per 100,000 persons compared with 13–60 per 100,000 among those without high-risk conditions (*7,9*). Despite the increased risk of severe illness, only an estimated 40%–41% of persons aged 50–64 years with chronic medical conditions and 28%–29% of those without high-risk conditions were vaccinated against influenza in 1997 (National Immunization Program, CDC, unpublished data, 2000). Age-based strategies have been more successful than patient-selection strategies based on medical conditions; thus, targeting all persons 50–64 years of age will likely increase vaccination rates among persons in this age group with high-risk conditions (*10,11*). In addition, this strategy will also likely help to increase vaccination of persons without high-risk conditions for whom annual vaccination is recommended because they live with or care for persons at increased risk of influenza-related complications.

Of the approximately 41 million persons in the United States aged 50–64 years, 28–31 million are without identified chronic underlying medical conditions (National Immunization Program, CDC, unpublished data, 2000). Although healthy adults are at low risk for severe illness, influenza can result in substantial morbidity, health-care provider visits, and lost work days. Vaccination of healthy adults aged <65 years can reduce the number of illnesses and physician visits, work absenteeism, and antibiotic use (*12–15*). Further, 50 years is an age when other preventive services begin and when routine assessment of vaccination and other preventive services has been recommended (*10*).

Vaccination Coverage Levels

Among persons aged ≥65 years, influenza vaccination levels increased from 33% in 1989 (*16*) to 63% in 1997 (*17*), surpassing the *Healthy People 2000* goal of 60% (*18*). Although influenza vaccination coverage increased in black, Hispanic, and white populations, vaccination levels among blacks and Hispanics continue to lag behind those among whites (*17,19*). Possible reasons for the increase in influenza vaccination levels among persons aged ≥65 years include greater acceptance of preventive medical services by practitioners, increased delivery and administration of vaccine by health-care providers and sources other than physicians, and the initiation of Medicare reimbursement for influenza vaccination in 1993 (*20*). The *Healthy People 2010* objective is to achieve vaccination coverage for 90% of persons aged ≥65 years (*21*).

In 1997, the vaccination rate for persons at high risk aged <65 years was <30%, far short of the *Healthy People 2000* goal of 60% (*17,22*), despite reported benefits of vaccination. Increasing vaccination coverage among persons at high risk aged <65 years now is the highest priority for expanding influenza vaccine use.

Although annual vaccination is recommended for health-care workers, in the 1997 National Health Interview Survey, only 34% of health-care workers reported that they received influenza vaccine (*23*). Vaccination of health-care workers has been associated with reduced work absenteeism (*13*) and decreased deaths among nursing home patients (*24,25*). Efforts should be made to educate health-care workers about 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.

Primary Changes in the Recommendations

These recommendations include five principal changes:

- The age for universal vaccination has been lowered to 50 years from 65 years.
- Scheduling of large, organized vaccination campaigns after mid-October may be considered because the availability of vaccine in any location cannot be assured consistently in the early fall.
- The 2000–2001 trivalent vaccine virus strains are A/Moscow/10/99 (H3N2)-like, A/New Caledonia/20/99 (H1N1)-like, and B/Beijing/184/93-like strains.
- Information on neuraminidase-inhibitor antiviral drugs has been added.
- A list of other influenza-related infection control documents for special populations has been added.

Influenza and Its Burden

Biology of Influenza

Influenza A and B are the two types of influenza viruses that cause epidemic human disease (*26*). Influenza A viruses are further categorized into subtypes based on two surface antigens: hemagglutinin (H) and neuraminidase (N). Influenza B viruses are not categorized into subtypes. Both influenza A and B viruses are further separated into groups based on 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. Since 1977, influenza A (H1N1) viruses, influenza A (H3N2) viruses, and influenza B viruses have been in global circulation. A person's immunity to the surface antigens, especially hemagglutinin, reduces the likelihood of infection and severity of disease if infection occurs (*27*). However, antibody against one influenza virus type or subtype confers little or no protection against another 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 (*28*). The 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

The incubation period for influenza is 1–4 days with an average of 2 days (*29*). 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) (*30*). Illness typically resolves after several days for most persons, although cough and malaise can persist for 2 or more weeks. In some persons, influenza can exacerbate underlying medical conditions (e.g., pulmonary or cardiac disease) or lead to secondary bacterial pneumonia or primary influenza viral pneumonia (*31*).

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 some underlying health conditions than among healthy older children and younger adults (*1,31–34*). Estimated rates of influenza-associated hospitalizations have varied substantially by age group in studies conducted during different influenza epidemics:

- Among children aged 0–4 years, rates have ranged from approximately 500 per 100,000 population for those with high-risk conditions to 100 per 100,000 population for those without high-risk conditions (*35*). Among children without high-risk conditions, rates differ substantially within the 0–4-year age group: babies aged <6 months have the highest hospitalization rate at approximately 1,040 per 100,000 population, and children aged 2–4 years are hospitalized at a rate of approximately 8–136 per 100,000 population (*36,37*).
- Among children aged 5–14 years, rates have ranged from approximately 200 per 100,000 population for those with high-risk conditions to 20–40 per 100,000 population for those without high-risk conditions (*35,37*).
- Among persons aged 15–44 years, rates have ranged from approximately 40–60 per 100,000 population for those with high-risk conditions to approximately 20–30 per 100,000 population for those without high-risk conditions (*6,7*).
- Among persons aged 45–64 years, rates have ranged from approximately 80–400 per 100,000 population for those with high-risk medical conditions to approximately 20–40 per 100,000 population for those without high-risk conditions (*7,35*).
- Among persons aged ≥65 years, rates have ranged from approximately 200 to >1,000 per 100,000 population (*7,35,38*).

During influenza epidemics from 1969–1970 through 1993–1994, the estimated overall number of influenza-associated hospitalizations in the United States has ranged from approximately 20,000 to >300,000 per epidemic. An analysis of national hospital discharge data indicates an average of approximately 114,000 excess hospitalizations per year are related to influenza. 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 (*39*).

During influenza epidemics, deaths can increase from influenza and 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 (*40*) (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 per 100,000 persons aged ≥65 years (Influenza Branch, DVRD, NCID, CDC, unpublished data 1998). These older adults currently account for >90% of the deaths attributed to pneumonia and influenza (*41*). From 1972–1973 through 1994–1995, more than 20,000 influenza-

associated deaths were estimated to occur during each of 11 different U.S. epidemics, and more than 40,000 influenza-associated deaths were estimated for each of six of these 11 epidemics (*40*) (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 (*42*).

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). In addition, 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).

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 high 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 (*43*). Vaccination of health-care workers and other persons in close contact with persons in high-risk groups can also help reduce transmission of influenza and subsequent influenza-related complications.

Effectiveness of Inactivated Influenza Vaccine

Influenza vaccine contains three strains (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) (*44*). Whole-virus, subvirion, and purified-surface–antigen preparations are available.

Most vaccinated children and young adults develop high postvaccination hemagglutination-inhibition antibody titers (*45,46*). These antibody titers are protective against illness caused by strains similar to those in the vaccine (*46–48*). 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. When the antigenic match between vaccine and circulating viruses is close, influenza vaccine prevents illness in approximately 70%–90% of healthy persons aged <65 years (*49*). Vaccination of healthy adults also has resulted in decreased work absenteeism and decreased use of health-care resources when the vaccine and circulating viruses are well matched (*13–15,50*). Other studies suggest that the use of trivalent inactivated influenza vaccine or live attenuated influenza vaccine decreases the incidence of otitis media and the use of antibiotics among children (*51–53*).

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 (*54–56*). However, among such persons, the vaccine can be effective in preventing secondary complications and reducing the risk for influenza-related hospitalization and death (*43,57,58*). 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 (*12,58*). Among elderly persons residing in nursing homes, influenza vaccine is most effective in preventing severe illness, secondary complications, and deaths. In 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% (*59,60*).

Composition of the 2000–2001 Influenza Vaccine

The trivalent influenza vaccine prepared for the 2000–2001 season will include A/Moscow/10/99 (H3N2)-like, A/New Caledonia/20/99 (H1N1)-like, and B/Beijing/184/93-like antigens. For the A/Moscow/10/99 (H3N2)-like antigen, U.S. manufacturers will use the antigenically equivalent A/Panama/2007/99 (H3N2) virus and for the B/Beijing/184/93-like antigen, they will use the antigenically equivalent B/Yamanashi/166/98 virus; these viruses will be used because of their growth properties and because they are representative of currently circulating A (H3N2) and B viruses.

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. Manufacturing processes differ by manufacturer. Some manufacturers might use additional compounds to inactivate the influenza viruses, and they might use an antibiotic to prevent bacterial contamination. The package inserts should be consulted for additional information.

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 in high-risk groups should be vaccinated to decrease the risk of 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

Groups at Increased Risk for Complications

Vaccination is recommended for the following groups of persons who are at increased risk for complications from influenza or who have a higher prevalence of chronic medical conditions that place them at risk for influenza-related complications:

- persons aged ≥50 years;
- residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions;
- adults and children who have chronic disorders of the pulmonary or cardiovascular systems, including asthma;
- adults and children who have required regular medical follow-up or

hospitalization during the preceding year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus);

- children and teenagers (aged 6 months to 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.

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 care givers to persons at high risk might reduce influenza-related deaths among persons at high risk. Evidence from two studies suggests that vaccination of health-care workers is associated with decreased deaths among nursing home patients (*24,25*). Vaccination of health-care workers and others in close contact with persons at high risk 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 high-risk groups;
- persons who provide home care to persons in high-risk groups;
- household members (including children) of persons in high-risk groups.

Additional Information on Vaccination of Specific Populations

Pregnant Women

Influenza-associated excess deaths among pregnant women were documented during the pandemics of 1918–1919 and 1957–1958 (*61–64*). 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 (*65–68*). 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 (*69*). Women in their third trimester of pregnancy were hospitalized at a rate (250 per 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, many 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 (*70*). However, more 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.

Persons Infected with Human Immunodeficiency Virus

Limited information is available regarding the frequency and severity of influenza illness or the benefits of influenza vaccination among persons with human immunodeficiency virus (HIV) infection (*71,72*). However, a recent 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 in the peri-influenza periods. The risk of hospitalization for HIV-infected women was higher than the risk for women with other well-recognized high-risk conditions for influenza complications, including chronic heart and lung diseases (*9*). Other reports suggest that influenza symptoms might be prolonged and the risk for complications from influenza increased for some HIV-infected persons (*73,74*).

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 (*75–78*). 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; few persons with CD4+ T-lymphocyte cell counts of <200 were included in this study (*72*). In patients who have advanced HIV disease and low CD4+ T-lymphocyte cell counts, influenza vaccine might not induce protective antibody titers (*77,78*); a second dose of vaccine does not improve the immune response in these persons (*78,79*).

One study found that HIV RNA levels increased transiently in one HIV-infected patient after influenza infection (*80*). Some 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 (*77,81*). Other studies using similar laboratory techniques have not documented a substantial increase in the replication of HIV (*82–84*). Deterioration of CD4+ T-lymphocyte cell counts or progression of HIV disease have not been demonstrated among HIV-infected persons following influenza vaccination. The effect of antiretroviral therapy on potential increases in HIV RNA levels following either natural influenza infection or influenza vaccination is unknown (*71*). Because influenza can result in serious illness and complications and because influenza

vaccination can result in the production of protective antibody titers, vaccination will benefit many 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 of 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, most influenza activity occurs from April through 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 from April through 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 of influenza and the advisability of carrying antiviral medications for either prophylaxis or treatment of influenza.

General Population

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 6 months). 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 the antiviral agents amantadine or rimantadine is an option for preventing influenza A 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 about 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.

Optimal Timing for Annual Vaccination

The optimal time to vaccinate persons in high-risk groups is usually from the beginning of October through mid-November, because influenza activity in the United States generally peaks between late December and early March. Although vaccine generally becomes available in August or September, in some years, vaccine for the upcoming influenza season might not be available in some locations until later in the fall. To minimize the possibility that large organized vaccination campaigns will need to be canceled because vaccine is unavailable, persons planning large organized vaccination campaigns may consider scheduling these events after mid-October because the availability of vaccine in any location cannot be assured consistently in the early fall. Administering vaccine before October should generally be avoided in facilities such as nursing homes, because antibody levels can begin to decline within a few months after vaccination (*85,86*).

Vaccination Outside of Optimal Period

To avoid missed opportunities for vaccination, beginning each September, influenza vaccine should be offered to persons at high risk when they are seen by health-care providers for routine care or are hospitalized, provided that vaccine is available. If regional influenza activity is expected to begin earlier than December, vaccination programs also can be undertaken as early as September. Health-care providers should offer vaccine to unvaccinated persons even after influenza virus activity is documented in a community and should continue to offer vaccine throughout the influenza season. (For information on vaccination of travelers, see Travelers.)

Dosage

Dosage recommendations vary according to age group (Table 1). Among previously unvaccinated children aged <9 years, two doses administered at least 1 month 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 (*87–90*). 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 (*85,86*). Vaccine prepared for a previous influenza season should not be administered to provide protection for the current season.

TABLE 1. Influenza vaccine* dosage, by age group — United States, 2000–2001 season

Age group	Product†	Dose	No. of doses	Route§
6–35 mos	Split-virus only	0.25 mL	1 or 2¶	IM**
3–8 yrs	Split-virus only	0.50 mL	1 or 2¶	IM
9–12 yrs	Split-virus only	0.50 mL	1	IM
>12 yrs	Whole- or split-virus	0.50 mL	1	IM

* Contains 15 µg each of A/Moscow/10/99 (H3N2)-like, A/New Caledonia/20/99 (H1N1)-like, and B/Beijing 184/93-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/Beijing/184/93-like antigen, U.S. manufacturers will use the antigenically equivalent B/Yamanashi/166/98 virus because of their growth properties and because they are representative of currently circulating A (H3N2) and B viruses. Manufacturers include Aventis Pasteur, Inc. (Fluzone® whole or split); Medeva Pharma Ltd. (Fluvirin™ purified surface antigen vaccine); Parkedale Pharmaceuticals, Inc. (Fluogen® split); and Wyeth Lederle Laboratories (Flushield™ split). For further product information call Aventis Pasteur, (800) 822-2463; Medeva, (800) 234-5535; Parkedale, (888) 358-6436; or Wyeth Lederle, (800) 358-7443.

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

§ 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 at least 1 month apart are recommended for children <9 years of age who are receiving influenza vaccine for the first time.

** IM = intramuscular.

Route

The intramuscular route is recommended for influenza vaccine. Adults and older children should be vaccinated in the deltoid muscle; a needle length ≥1 inch can be considered for these age groups. Infants and young children should be vaccinated in the anterolateral aspect of the thigh (*91*).

Side Effects and Adverse Reactions

When educating patients about 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 up to 2 days (*92–94*). 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 exposure to the influenza virus antigens in the vaccine (e.g., young children) (*95,96*). These reactions begin 6–12 hours after vaccination and can persist for 1–2 days. Recent placebo-controlled trials suggest 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 (*92–94*).

Immediate — presumably allergic — reactions (e.g., hives, angioedema, allergic asthma, and systemic anaphylaxis) rarely occur after influenza vaccination (*97*). 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 (*98,99*).

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 (*100,101*). When reported, hypersensitivity to thimerosal usually has consisted of local, delayed-type hypersensitivity reactions (*100*).

Guillain-Barré Syndrome

The 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré syndrome (GBS) (*102,103*). Among persons who received the swine influenza vaccine in 1976, the rate of GBS that exceeded the background rate was slightly less than 10 cases per million persons vaccinated. Evidence for a causal relationship of GBS with subsequent vaccines prepared from other influenza viruses is less clear. Obtaining strong epidemiologic evidence for a possible small increase in risk is difficult for a rare condition such as GBS, which has an annual incidence of only 10–20 cases per million adults (*104*), and stretches the limits of epidemiologic investigation. More definitive data probably will require the use of other methodologies, such as laboratory studies of the pathophysiology of GBS.

During three of four influenza seasons studied from 1977 through 1991, the overall relative risk estimates for GBS after influenza vaccination were slightly elevated but were not statistically significant in any of these studies (*105–107*). 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 following vaccination, representing an excess of slightly more than one additional case of GBS per million persons vaccinated; the combined number of GBS cases peaked 2 weeks after vaccination (*108*). Thus, investigations to date suggest no large 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 quite small — slightly more than one additional case per million persons vaccinated. Cases of GBS following influenza infection have been reported, but no epidemiologic studies have documented such an association (*109,110*). Good evidence exists that several infectious illnesses, most notably *Campylobacter jejuni,*

as well as upper respiratory tract infections in general are associated with GBS (*104,111–113*).

Even if GBS were a true side effect of vaccination in the years after 1976, the estimated risk for GBS of slightly more than one additional case per million persons vaccinated is substantially less than the risk for severe influenza, which could be prevented by vaccination in all age groups, especially persons aged ≥65 years and those who have medical indications for influenza vaccination. During different epidemics occurring from 1972 through 1981, estimated rates of influenza-associated hospitalization have ranged from approximately 200 to 300 hospitalizations per million population for previously healthy persons aged 5–44 years and from 2,000 to >10,000 hospitalizations per million population for persons aged ≥65 years (*6,7,35,38*). During epidemics from 1972–1973 through 1994–1995, estimated rates of influenza-associated death have ranged from approximately 300 to >1,500 per million persons aged ≥65 years, who account for more than 90% of all influenza-associated deaths (see Introduction for more information about influenza-associated illness and death). 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 (*104,114*). However, no evidence indicates that the case-fatality ratio for GBS differs among vaccinated persons and those not vaccinated.

The incidence of GBS in the general population is very low, but persons with a history of GBS have a substantially greater likelihood of subsequently developing GBS than persons without such a history (*105,115*). 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, it would seem prudent to avoid 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. However, many experts believe that 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 (*116*). 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 (*117,118*). However, influenza vaccine is administered each year, whereas pneumococcal vaccine is not. 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 (usually by medical record review), use of reminder/recall systems, and efforts to remove administrative and financial barriers that prevent persons from receiving the vaccine (*119*). Use of standing orders programs are 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 (*120*). Persons for whom influenza vaccine is recommended can be identified and vaccinated in the settings described in the following paragraphs.

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 vaccine. Vaccine should be offered during visits beginning in September and throughout the influenza season. The offer of vaccine 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 vaccine to persons for whom vaccination is recommended or provide written information on 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 from September through March should be offered and strongly encouraged to receive influenza vaccine before they are discharged.

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. Care givers and other persons in the household (including children) should be referred for vaccination.

Other Facilities Providing Services to Persons Aged ≥50 Years

Facilities such 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 vaccine to all personnel, including night and weekend staff. Particular emphasis should be placed on persons who care for members of high-risk groups.

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 (*121–125*). 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 (*124,125*). 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). The 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 (*126*). 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 (*51*). In a follow-up study during the 1997–1998 season, the trivalent LAIV was 86% effective in preventing culture-positive influenza in children, despite a poor match between the vaccine's influenza A (H3N2) component and the predominant circulating influenza A (H3N2) virus (*127*). 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 (*128*). 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 in young children as well as the

potential safety issues and logistic and economic consequences of recommending routine vaccination of young healthy children.

Several studies indicate that rates of hospitalization are higher among young children than older children when influenza viruses are in circulation (*35,38,129,130*). The increased rates of hospitalization are comparable with rates for other high-risk groups. However, the interpretation of these findings has been confounded by cocirculation of respiratory syncytial viruses, which are a major cause of serious respiratory viral illness among children and which frequently circulate during the same time as influenza viruses (*131–133*). 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 <2 years of age, and possibly children 2–4 years of age, are at increased risk for influenza-related hospitalization compared with older healthy children.

RECOMMENDATIONS FOR THE USE OF ANTIVIRAL AGENTS FOR INFLUENZA

Antiviral drugs for influenza are an important adjunct to influenza vaccine for the control and prevention of influenza. However, they are not a substitute for vaccination. Four currently licensed 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 in adults and children aged ≥1 year. Rimantadine was approved in 1993 for treatment and prophylaxis of infection in adults. Although rimantadine was approved only for prophylaxis of infection in children, many experts consider it appropriate for treatment among children.

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, but neither have yet been approved for prophylaxis. Zanamivir was approved for treatment for persons aged ≥12 years, and oseltamivir was approved for treatment for persons aged ≥18 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; however, readers should consult the package inserts for more information.

Role of Laboratory Diagnosis

The appropriate treatment of patients with respiratory illness depends on accurate and timely diagnosis. The early diagnosis of influenza can help reduce the inappropriate use of antibiotics and provide the option of using antiviral therapy. However, because some 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 (e.g., viral culture and rapid tests for influenza) can aid clinical judgment and help guide treatment decisions.

Influenza surveillance by state and local health departments and CDC can provide information about the presence of influenza viruses in the community. Surveillance can also identify the predominant circulating types, subtypes, and strains of influenza.

Several commercial rapid diagnostic tests are available that can be used by laboratories in outpatient settings to detect influenza viruses within 30 minutes (*29,134*). Some of these rapid tests detect only influenza A viruses, whereas other rapid tests detect both influenza A and B viruses but do not distinguish between the two types. Additional commercial diagnostic tests are available for use by laboratories performing tests of high complexity (*29*).

Despite the availability of rapid diagnostic tests, the collection of clinical specimens for viral culture is important because only culture isolates can provide specific information on circulating influenza subtypes and strains. This information is needed to compare current circulating influenza strains with vaccine strains, to guide decisions about influenza treatment and prophylaxis, and to formulate vaccine for the coming year. Virus isolates also are needed to monitor the emergence of antiviral resistance.

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 (*135–144*). 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 (*137,145,146*). However, in vitro data (*147–152*) and data from studies of treatment in mice and ferrets (*149,150,153,154*) document that zanamivir and oseltamivir have activity against influenza B viruses.

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 (*155*). Data are limited and inconclusive concerning the effectiveness of amantadine, rimantadine, and zanamivir for treatment of influenza in persons at high risk for serious complications of influenza (*135,137,138,140,156–159*), and no published data are available concerning the effectiveness of oseltamivir for treatment of influenza in high-risk populations. Studies of the efficacy of any of the four drugs for treatment in children are limited (*135, 159–161*).

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 important 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 (*135,144,159*). 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, some 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 (*135*). Both drugs have been studied extensively in nursing home populations as a component of influenza outbreak control programs (*135,158,162–164*).

Zanamivir and oseltamivir have not been approved for prophylaxis, but recent community studies suggest that both drugs are similarly effective in preventing febrile, laboratory-confirmed influenza illness (efficacy: zanamivir, 84%; oseltamivir, 82%) (*165,166*). Experience with prophylactic use of these agents in institutional settings or among patients with chronic medical conditions is limited (*167–169*). Use of zanamivir has not been found to impair the immunologic response to influenza vaccine (*170,171*).

When determining the timing and duration for administering amantadine or rimantadine 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, amantadine or rimantadine prophylaxis should be taken only during the period of peak influenza activity in a community (*172*).

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 (*173,174*). When influenza vaccine is given while influenza A viruses are circulating, chemoprophylaxis with amantadine or rimantadine 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 with amantadine or rimantadine during peak influenza A 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 A 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 human immunodeficiency virus (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 amantadine or rimantadine 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. Amantadine or rimantadine also can be administered prophylactically to persons who wish to avoid influenza A illness. Health-care providers and patients should make this decision on an individual basis.

Control of Influenza Outbreaks in Institutions

Most published reports on the use of amantadine or rimantadine to control institutional outbreaks of influenza A are based on studies of nursing home populations. When confirmed or suspected outbreaks of influenza A 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 vaccine during the previous fall — and should continue for at least 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 A that is not well matched by the vaccine.

Chemoprophylaxis has been used successfully to control an influenza A outbreak aboard a large cruise ship (*175*). Chemoprophylaxis also can be considered for controlling influenza A outbreaks in other closed or semiclosed settings (e.g., dormitories or other settings where persons live in close proximity).

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 antiviral drugs for treatment and other persons, including those taking chemoprophylaxis. In addition to using antiviral drugs for treatment and prophylaxis of influenza, other outbreak control measures include instituting droplet precautions and establishing cohorts of patients with confirmed or suspected influenza, reoffering influenza vaccine to unvaccinated staff and patients, restricting staff movement between wards or buildings, and restricting contact between ill staff or visitors and patients (*176–178*). (For more information on outbreak control in specific settings, refer to additional references in Additional Information on Influenza Infection Control in Specific Populations.)

Dosage

Dosage recommendations vary by age group and medical conditions (Table 2).

TABLE 2. Recommended daily dosage of influenza antiviral medications for treatment and prophylaxis

Antiviral agent	Age group 1–9 yrs	10–13 yrs	14–64 yrs	≥65 yrs
Amantadine*				
Treatment	5 mg/kg/day up to 150 mg† in two divided doses	100 mg twice daily§	100 mg twice daily	≤100 mg/day
Prophylaxis	5 mg/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	100 mg twice daily	100 or 200 mg/day††
Prophylaxis	5 mg/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
Prophylaxis¶¶	NA	NA	NA	NA
Oseltamivir				
Treatment***	NA	NA	75 mg*** twice daily	75 mg twice daily
Prophylaxis¶¶	NA	NA	NA	NA

NOTE: Amantadine manufacturers include Endo Pharmaceuticals (Symmetrel® — tablet and syrup); Invamed 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 (Tamiflu® — tablet).

* Consult the drug package insert 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 ≥10 years of age 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.

** NA = Not applicable.

†† Elderly nursing home residents should be administered only 100 mg/day of rimantadine. A reduction in dosage to 100 mg/day should be considered for all persons ≥65 years of age if they experience possible side effects when taking 200 mg/day.

§§ Zanamivir is approved for persons ≥12 years of age and is administered as two 5-mg inhalations of medicated powder twice a day (i.e., 10 mg twice a day). The medication is administered via inhalation using a plastic device included in the package with the medication. Patients will benefit from instruction and demonstration of proper use of the device.

¶¶ Neither zanamivir nor oseltamivir are approved for prophylaxis.

*** Oseltamivir is approved for persons ≥18 years of age. A reduction in the dose of oseltamivir is recommended for persons with creatinine clearance <30 mL/min.

Children

Amantadine

The use of amantadine among children aged <1 year has not been adequately evaluated. The U.S. Food and Drug Administration-approved dosage for children aged 1–9 years 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 (*179*).

Rimantadine

The use of rimantadine among children aged <1 year has not been adequately evaluated. For children aged 1–9 years, rimantadine should be administered in one or two divided doses at a dosage of 5 mg/kg/day, not to exceed 150 mg/day. 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 (*180*).

Zanamivir

Zanamivir is not approved for use in children aged <12 years. The recommended dosage of zanamivir for treatment of influenza in persons aged ≥12 years is two inhalations (one 5-mg blister per inhalation for a total dose of 10 mg) twice daily (approximately 12 hours apart) for 5 days (*170*).

Oseltamivir

Oseltamivir is not approved for use in persons aged <18 years (*181*).

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 some 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 (*182*). However, chronically ill elderly persons have had a higher incidence of CNS and gastrointestinal symptoms and serum concentrations two to four times higher than in healthy, younger persons when rimantadine has been administered at a dosage of 200 mg/day (*135*).

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 based on creatinine clearance are found in the packet insert. Because recommended dosages based on 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 (*183*).

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 (*184*).

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 (*170,185*). 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 (*186,187*). 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 (*170*).

Oseltamivir

Serum concentrations of oseltamivir carboxylate (GS4071), the active metabolite of oseltamivir, increase with declining renal function (*146,181*). A reduction of the dose of oseltamivir to 75 mg once daily is recommended for patients with creatinine clearance <30 mL/min (*181*). No data are available concerning the safety or efficacy of oseltamivir in patients with creatinine clearance <10 mL/min.

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 in patients receiving amantadine have been reported, although a specific relationship between the drug and such changes has not been established (*188*).

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 in 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 (*189*). 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 (*190*). The extent to which rimantadine might increase the incidence of seizures among persons with seizure disorders has not been adequately evaluated.

Zanamivir and Oseltamivir

No information is available regarding the use of zanamivir or oseltamivir among persons with a history of seizure disorder.

Route

Amantadine, rimantadine, and oseltamivir are administered orally. Amantadine and rimantadine are available in tablet or syrup form, and oseltamivir is available as a capsule (*179–181*). 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 proper use of this device (*170*).

Pharmacokinetics

Amantadine

More than 90% of amantadine is excreted unchanged in the urine by glomerular filtration and tubular secretion (*162,191–194*). Thus, renal clearance of amantadine is reduced substantially in persons with renal insufficiency, and dosages might need to be decreased (see Dosage) (Table 2).

Rimantadine

Approximately 75% of rimantadine is metabolized by the liver (*159*). The safety and pharmacokinetics of rimantadine among persons with liver disease have been evaluated only after single-dose administration (*159,195*). In a study of persons with chronic liver disease (most with stabilized cirrhosis), no alterations in liver function were observed after a single dose (*159,195*). However, for persons with severe liver dysfunction, the apparent clearance of rimantadine was 50% lower than that reported for persons without liver disease (*180*).

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 (*159,184*). 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 in healthy persons of the same age (*184*). 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 (*180,196*).

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 (*197,198*). 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 (*170,187*).

Oseltamivir

Approximately 80% of orally administered oseltamivir is absorbed systemically (*146*). 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 (*181,199*). Unmetabolized oseltamivir also is excreted in the urine by glomerular filtration and tubular secretion (*199*).

Side Effects and Adverse Reactions

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, the incidence of CNS side effects (e.g., nervousness, anxiety, difficulty concentrating, and lightheadedness) is higher among persons taking amantadine than among those taking rimantadine (*200*). In a 6-week study of prophylaxis among healthy adults, approximately 6% of participants taking rimantadine at a dosage of 200 mg/day experienced at least one CNS symptom, compared with approximately 13% of those taking the same dosage of amantadine and 4% of those taking placebo (*200*). A study of elderly persons also demonstrated fewer CNS side effects associated with rimantadine compared with amantadine (*182*). 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 (*200*).

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 sei-

zures) (*189*). 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 (*162*). 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 2). In acute overdosage of amantadine, CNS, renal, respiratory, and cardiac toxicity, including arrhythmias, have been reported (*179*). Because rimantadine has been marketed for a shorter period than amantadine, its safety in certain patient populations (e.g., chronically ill and elderly persons) has been evaluated less frequently.

When considering amantadine or rimantadine (i.e., choice of antiviral drug, dose, and duration of therapy), clinicians must take into account the patient's age, weight, and renal function (Table 2); the presence of other medical conditions; indications for the use of amantadine or rimantadine (i.e., prophylaxis or therapy); and the potential for interaction with other medications.

Zanamivir

Preliminary results of a study of zanamivir treatment of influenza-like illness among persons with asthma or chronic obstructive pulmonary disease indicated that more patients receiving zanamivir than placebo experienced a >20% decline in forced expiratory volume in 1 second (FEV1) or peak expiratory flow rates after treatment (*170*). Moreover, in a phase I study of persons with mild or moderate asthma who did not have influenza-like illness, one of 13 patients experienced bronchospasm following administration of zanamivir (*170*). In addition, during postmarketing surveillance, cases of respiratory function deterioration following inhalation of zanamivir have been reported among patients with underlying asthma or chronic obstructive pulmonary disease (*155*). 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 (*155*). 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 (*170*). 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 (*155*).

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) (*136–141,170,197*). 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 (*136,137,139,140,170*). Each of these symptoms was reported by <5% of persons in the clinical treatment studies combined (*170*).

Oseltamivir

Nausea and vomiting were reported more frequently among persons receiving oseltamivir for treatment (nausea without vomiting, approximately 10%; vomiting, approximately 9%) than among persons receiving placebo (nausea without vomiting, ap-

proximately 6%; vomiting, approximately 3%) (*142,143,181,201*). However, few persons enrolled in the clinical treatment trials of oseltamivir discontinued treatment because of these symptoms (*181*). Nausea and vomiting might be less severe if oseltamivir is taken with food (*181,201*).

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 (*68,202*). However, both amantadine and rimantadine have been shown in animal studies to be teratogenic and embryotoxic when administered at very high doses (*179,180*). 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 [*170,179–181*]).

Drug Interactions

Careful observation is advised when amantadine is administered concurrently with drugs that affect the CNS, especially CNS stimulants. Concomitant administration of antihistamines or anticholinergic drugs can increase the incidence of adverse CNS reactions (*135*). 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 (*170,203*).

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 (*181,199*).

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, the package inserts should be consulted.

Antiviral Drug-Resistant Strains of Influenza

Amantadine-resistant viruses are cross-resistant to rimantadine and vice versa (*204*). Drug-resistant viruses can appear in up to approximately one third of patients when either amantadine or rimantadine is used for therapy (*161,205*). During the course of amantadine or rimantadine therapy, resistant influenza strains can replace sensitive strains within 2–3 days of starting therapy (*205,206*). 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 (*207,208*); 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 (*209*). The screening of epidemic strains of influenza A has rarely detected amantadine- and rimantadine-resistant viruses (*205,210,211*).

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 (*161*). 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 (*212–219*), 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 (*220,221*). Whether these in vitro findings indicate that clinical drug resistance will occur less frequently with zanamivir and oseltamivir than with amantadine and rimantadine is unknown. Development of viral resistance to zanamivir and oseltamivir during treatment has been identified but does not appear to be frequent (*138,181,222,223*). 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. Postmarketing surveillance for neuraminidase inhibitor-resistant influenza viruses is planned.

SOURCES OF INFORMATION ON INFLUENZA AND ITS SURVEILLANCE

Information regarding influenza surveillance is available through the CDC Voice Information System (influenza update), (888) 232-3228; CDC Fax Information Service, (888) 232-3299; or website for the Influenza Branch, DVRD, NCID, CDC at <http://www.cdc.gov/ncidod/diseases/flu/weekly.htm>. From October through May, the information is updated at least every other week. In addition, periodic updates about 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 about state or local influenza activity, and for reporting influenza outbreaks and receiving advice regarding outbreak control.

ADDITIONAL INFORMATION ON INFLUENZA INFECTION CONTROL IN SPECIFIC POPULATIONS

Each year, the Advisory Committee on Immunization Practices provides general, annually updated information about the control and prevention of influenza. Other documents on the control and prevention of influenza in specific populations (e.g., immunocompromised persons, health-care workers, hospitals, and travelers) are also available:

- Garner JS. Hospital Infection Control Practices Advisory Committee. Guideline for isolation precautions in hospitals. Infect Control Hosp Epidemiol 1996;17:53–80.
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- Bolyard EA, Tablan OC, Williams WW, et al., Hospital Infection Control Practices Advisory Committee. Guideline for infection control in health care personnel. Am J Infect Control 1998;26:289–354.
- Bradley SF, The Long-Term–Care Committee of the Society for Healthcare Epidemiology of America. Prevention of influenza in long-term care facilities. Infect Control Hosp Epidemiol 1999;20:629–37.
- American Academy of Pediatrics. 2000 red book: report of the Committee on Infectious Diseases. 25th edition. Elk Grove Village, IL: American Academy of Pediatrics, 2000 (in press).
- CDC. 1999 USPHS/IDSA Guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. MMWR 1999;48(No. RR-10):1–59.
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- 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: National Center for Infectious Diseases, CDC, 1999.
- CDC. Preventing influenza A infection among travelers. Available at <http://www.cdc.gov/travel/feb99.htm>. Accessed March 10, 2000.

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CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

MMWR™
MORBIDITY AND MORTALITY
WEEKLY REPORT

April 14, 2000 / Vol. 49 / No. RR-3

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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1. Read this *MMWR* (Vol. 49, RR-3), which contains the correct answers to the questions beginning on the next page.
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Continuing Nursing Education (CNE). This activity for 1.3 contact hours is provided by CDC, which is accredited as a provider of continuing education in nursing by the American Nurses Credentialing Center's Commission on Accreditation.

GOAL AND OBJECTIVES

This *MMWR* provides recommendations regarding the prevention and control of influenza. These recommendations were developed by CDC staff members and the Influenza Working Group of the 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 not true concerning the burden of influenza in the United States?**
   - A. The greatest number of influenza-related hospitalizations occur during epidemics of influenza A (H3N2).
   - B. Persons 65 years of age and older account for more than 90% of deaths from influenza.
   - C. On average, more than 100,000 influenza-related hospitalizations occur each year.
   - D. Pneumonia and influenza-related deaths have decreased substantially in the United States in recent years.
   - E. More than 40,000 influenza-associated deaths have occurred during each of six recent influenza epidemics.

2. **What is the main option for reducing the impact of influenza in the United States?**
   - A. Influenza vaccine.
   - B. Antiviral agents.
   - C. Antibiotics.
   - D. Vitamin supplements.
   - E. Smoking cessation programs.

3. **Which of the following is not true concerning influenza vaccine?**
   - A. Influenza vaccine contains three strains of influenza virus.
   - B. Influenza vaccine viruses are grown in eggs.
   - C. Influenza vaccine has been shown to be 70%–90% effective in preventing influenza among healthy persons <65 years of age.
   - D. Among elderly persons, influenza vaccine is more effective in reducing complications of influenza than in preventing influenza illness.
   - E. Influenza vaccine effectiveness is entirely dependent on the similarity between strains of virus in the vaccine and those in circulation.

4. **Which of the following best describes the currently licensed influenza vaccine?**
   - A. Live attenuated virus.
   - B. Inactivated virus.
   - C. Reassortant.
   - D. Toxoid.
   - E. Cloned DNA.

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

   A. Persons aged ≥50 years.
   B. Health-care providers.
   C. Children with asthma.
   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.

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

   A. Unvaccinated children <9 years of age receiving influenza vaccine for the first time.
   B. Health-care workers.
   C. Elderly persons who reside in extended care facilities.
   D. Persons with human immunodeficiency virus infection.
   E. All of the above groups should receive two doses of influenza vaccine during the same season.

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

   A. Infection with human immunodeficiency virus.
   B. Severe allergy to a component of the vaccine.
   C. Recent administration of antibody-containing blood product (e.g., whole blood or immune globulin).
   D. Current administration of antibiotics.
   E. All of the above are valid contraindications or precautions for the use of influenza vaccine.

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

   A. Allergic reactions, such as angioedema.
   B. Fever.
   C. An illness identical to influenza.
   D. Soreness at the injection site.
   E. Guillain-Barré syndrome.

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

   A. All influenza antiviral agents are equally effective against influenza A and B viruses.
   B. Influenza antiviral agents are approved only for the treatment of influenza A infection.
   C. Antiviral agents significantly reduce the response to influenza vaccine.
   D. Antiviral agents have not been shown to be effective in preventing serious influenza-related complications.
   E. Treatment of influenza with antiviral agents requires a course of therapy of at least 14 days.

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 or urgent care.
B. Patient care — inpatient.
C. Patient care — primary care clinic or office.
D. Laboratory or 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, approximately how many persons do you administer influenza vaccine to?

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

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

A. 1–1.5 hours.
B. More than 1.5 hours but fewer than 2 hours.
C. 2 or more 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 licensed 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.

Correct answers for questions 1–9

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

MMWR Response Form for Continuing Education Credit
April 14, 2000/Vol. 49/No. RR-3

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To receive continuing education credit, you must
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Check One
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Fill in the appropriate blocks to indicate your answers. Remember, you must answer <u>all</u> of the questions to receive continuing education credit!

1. [ ] A [ ] B [ ] C [ ] D [ ] E
2. [ ] A [ ] B [ ] C [ ] D [ ] E
3. [ ] A [ ] B [ ] C [ ] D [ ] E
4. [ ] A [ ] B [ ] C [ ] D [ ] E
5. [ ] A [ ] B [ ] C [ ] D [ ] E
6. [ ] A [ ] B [ ] C [ ] D [ ] E
7. [ ] A [ ] B [ ] C [ ] D [ ] E
8. [ ] A [ ] B [ ] C [ ] D [ ] E
9. [ ] A [ ] B [ ] C [ ] D [ ] E
10. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F
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13. [ ] A [ ] B [ ] C [ ] D [ ] E [ ] F
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16. [ ] A [ ] B [ ] C [ ] D [ ] E
17. [ ] A [ ] B [ ] C [ ] D [ ] E
18. [ ] A [ ] B [ ] C [ ] D [ ] E
19. [ ] A [ ] B [ ] C [ ] D [ ] E
20. [ ] A [ ] B [ ] C [ ] D [ ] E
21. [ ] A [ ] B [ ] C [ ] D [ ] E
22. [ ] A [ ] B [ ] C [ ] D [ ] E

Signature ***Date I Completed Exam***

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