VIRGINIA
EPIDEMIOLOGY BULLETIN

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

The following article is adapted from the MMWR article with the above title (1998;47[No. RR-6]:1-26). If you would like to receive a copy of the entire MMWR article, you may call the Office of Epidemiology at 804/786-6261 or visit the Centers for Disease Control and Prevention web site at http://www.cdc.gov.

INTRODUCTION

Influenza A viruses are classified into subtypes on the basis of two surface antigens: hemagglutinin (H) and neuraminidase (N). Three subtypes of hemagglutinin (H1, H2, and H3) and two subtypes of neuraminidase (N1 and N2) are recognized among influenza A viruses that have caused widespread human disease. Immunity to these antigens, especially to the hemagglutinin, reduces the likelihood of infection and lessens the severity of disease if infection occurs. Infection with a virus of one subtype confers little or no protection against viruses of other subtypes. Furthermore, over time, antigenic variation (antigenic drift) within a subtype may be so marked that infection or vaccination with one strain may not induce immunity to distantly related strains of the same subtype. Although influenza B viruses have shown more antigenic stability than influenza A viruses, antigenic variation does occur. For these reasons, major epidemics of respiratory disease caused by new variants of influenza continue to occur. The antigenic characteristics of circulating strains provide the basis for selecting the virus strains included in each year's vaccine.

Typical influenza illness is characterized by abrupt onset of fever, myalgia, sore throat, and nonproductive cough. Unlike other common respiratory illnesses, influenza can cause

severe malaise lasting several days. More severe illness can result if either primary influenza pneumonia or secondary bacterial pneumonia occurs. During influenza epidemics, high attack rates of acute illness result in both increased numbers of visits to physicians' offices, walk-in clinics, and emergency rooms and increased hospitalizations for management of lower respiratory tract complications.

Elderly persons and persons with underlying health problems are at increased risk for complications of influenza. If they become ill with influenza, such members of high-risk groups are more likely than the general population to require hospitalization. During major epidemics, hospitalization rates for persons at high risk may increase substantially, depending on the age group. Previously healthy children and younger adults also may require hospitalization for influenza-related complications, but the relative increase in their hospitalization rates during epidemics is less than for persons who belong to high-risk groups.

During influenza epidemics from 1969-70 through 1993-94, the estimated number of influenza-associated hospitalizations has ranged from approximately 20,000 to >300,000 per epidemic, with an average of approximately 130,000-170,000 per epidemic. The greatest numbers of influenza-associated hospitalizations have occurred during epidemics caused by type A (H3N2) viruses, with an estimated average of 160,000-200,000 excess hospitalizations per epidemic.

An increase in mortality further indicates the impact of influenza epidemics. Increased mortality results not only from influenza and pneumonia but also from cardiopulmonary and other chronic diseases that can be exacerbated by influenza.

Pneumonia and influenza deaths may be increasing because the number of elderly persons in the U.S. population is increasing, as well as the number of persons aged <65 years at increased risk for influenza related complications (e.g., organ-transplant recipients, neonates in intensive-care units, and persons who have cystic fibrosis and acquired immunodeficiency syndrome [AIDS], all of whom have longer life expectancies than in previous years).

Influenza vaccination campaigns are targeted to approximately 34 million persons aged ≥65 years and 27 million to 31 million persons aged <65 years who are at high risk for influenza-associated complications. Na-

tional health objectives for the year 2000 include vaccination of at least 60% of persons at risk for severe influenza-related illness.

Influenza vaccination levels among persons aged ≥65 years increased substantially from 1985 (23%) to 1995 (58%), although vaccination levels among persons aged <65 years at high risk for influenza are estimated to be less than 30%. Possible reasons for the increase in influenza vaccination levels, especially 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.

OPTIONS FOR THE CONTROL OF INFLUENZA

In the United States, two measures are available that can reduce the impact of influenza: immunoprophylaxis with inactivated (i.e., killed-virus) vaccine and chemoprophylaxis or therapy with an influenza-specific antiviral drug (amantadine or rimantadine). Vaccinating persons at high risk before the influenza season each year is the most effective measure for reducing the impact of influenza. Vaccination can be highly cost effective when it is a) directed at persons who are most likely to experience complications or who are at increased risk for exposure and b) administered to persons at high risk during hospitalizations or routine health-care visits before the influenza season, thus making special visits to physicians' offices or clinics unnecessary.

INACTIVATED VACCINE FOR INFLUENZA A AND B

Each year's influenza vaccine contains three virus strains (usually two type A and one type B) representing the influenza viruses that are 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 (inactivated). Influenza vaccine rarely causes systemic or febrile reactions. Whole-virus, subvirion, and purified-surface-antigen preparations are available.

Most vaccinated children and young adults develop high postvaccination hemagglutination-inhibition antibody titers. These antibody titers are protective against illness caused by strains similar to those in the vaccine or the related variants that may emerge during outbreak periods. Elderly persons and persons with certain chronic diseases may develop lower postvaccination antibody titers than healthy young adults and thus may remain susceptible to influenza-related upper respiratory tract infection. However, even if such persons develop influenza illness despite vaccination, the vaccine can be effective in preventing lower respiratory tract involvement or other secondary complications, thereby reducing the risk for hospitalization and death.

The effectiveness of influenza vaccine in preventing or attenuating illness varies, depending primarily on the age and immunocompetence of the vaccine recipient and the degree of similarity between the virus strains included in the vaccine and those that circulate during the influenza season. When a good match exists between vaccine and circulating viruses, influenza vaccine has been shown to prevent illness in approximately 70%-90% of healthy persons aged <65 years. In these circumstances, studies also have indicated that the effectiveness of influenza vaccine in preventing hospitalization for pneumonia and influenza among elderly persons living in settings other than nursing homes or similar chronic-care facilities ranges from 30% to 70%.

Among elderly persons residing in nursing homes, influenza vaccine is most effective in preventing severe illness, secondary complications, and death. Studies of this population have indicated that the vaccine can be 50%-60% effective in preventing hospitalization and pneumonia and 80% effective in preventing death, even though efficacy in preventing influenza illness may often be in the range of 30%-40% among the frail elderly. Achieving a high rate of vaccination among nursing home residents can reduce the spread of infection in a facility, thus preventing disease through herd immunity. Vaccination of health-care workers in nursing homes also has been effective in reducing the impact of influenza among residents.

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. Health-care workers and others (including household members) in close contact with persons in high-risk groups also should be vaccinated. In addition, influenza vaccine may be administered to any person who wishes to reduce the chance of becoming infected with influenza (the vaccine can be administered to children as young as 6 months). The trivalent influenza vaccine prepared for the 1998-99 season will include A/Beijing/262/95-like (HlN1), A/Sydney/5/97-like (H3N2), and B/Beijing/184/93-like hemagglutinin antigens. For the B/Beijing/184/93-like antigen, U.S. manufacturers will use the antigenically equivalent strain B/Harbin/07/94 because of its growth properties. Dosage recommendations vary according to age group (Table 1).

Although the current influenza vaccine can contain 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. Because the 1998-99 vaccine differs from the 1997-98 vaccine, supplies of 1997-98 vaccine should not be administered to provide protection for the 1998-99 influenza season.

Vaccinating persons at high risk before the influenza season each year is the most effective measure for reducing the impact of influenza.

Two doses administered at least 1 month apart may be required for satisfactory antibody responses among previously unvaccinated children aged <9 years; however, studies of vaccines similar to those being used currently have indicated little or no improvement in antibody response when a second dose is administered to adults during the same season.

During recent decades, data on influenza vaccine immunogenicity and side effects have been obtained for intramuscularly administered vaccine. Because recent influenza vaccines have not been adequately evaluated when administered by other routes, the intramuscular route is recommended. Adults and older children should be vaccinated in the deltoid muscle and infants and young children in the anterolateral aspect of the thigh.

TARGET GROUPS FOR SPECIAL VACCINATION PROGRAMS

Groups at Increased Risk for Influenza-Related Complications:

- Persons aged ≥65 years;
- Residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions;
- Adults and children who have chronic disorders of the pulmonary or cardiovascular systems, including children with 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);
- Children and teenagers (aged 6 months-18 years) who are receiving long-term aspirin therapy and therefore might be at risk for developing Reye syndrome after influenza;
- Women who will be in the second or third trimester of pregnancy during the influenza season.

Influenza-associated excess mortality among pregnant women has not been documented except during the pandemics of 1918-19 and 1957-58. However, because death-certificate data often do not indicate whether a woman was pregnant at the time of death, studies conducted during interpandemic periods may underestimate the impact of influenza in this population. Case reports and limited studies suggest that pregnancy may 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. A recent 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 increased from 1.4 during weeks 14-20 of gestation to 4.7 during weeks 37-42 when their hospitalization rates were compared with rates among women who were 1-6 months postpartum. Women in their third trimester of pregnancy were hospitalized at a rate comparable to that of nonpregnant women who have high-risk medical conditions for whom influenza vaccine has traditionally been recommended. Using data from this study, researchers estimated that an average of 1 to 2 hospitalizations among pregnant women could be prevented for every 1,000 pregnant women vaccinated.

On the basis of these and other data that suggest that influenza infection may cause increased morbidity among women during the second and third trimesters of pregnancy, the Advisory Committee on Immunization Practices (ACIP) recommends that women who will be beyond the first trimester of pregnancy (≥14 weeks' gestation) during the influenza season 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. Studies of influenza vaccination of more than 2,000 pregnant women have demonstrated no adverse fetal effects associated with influenza vaccine; however, more data are needed. Because currently available influenza vaccine is not a live-virus vaccine and major systemic reactions to it are rare, many experts consider influenza vaccination safe during any stage of pregnancy. However, because spontaneous abortion is common in the first trimester and unnecessary exposures have traditionally been avoided during this time, some experts prefer influenza vaccination during the second trimester to avoid coincidental association of the vaccine with early pregnancy loss.

Groups that Can Transmit Influenza to Persons at High Risk

Persons who are clinically or subclinically infected can transmit influenza virus to persons at high risk whom they care for or live with. Some persons at high risk (e.g., the elderly, transplant recipients, and persons with AIDS) can have a low antibody response to influenza vaccine. Efforts to protect these members of high-risk groups against influenza might be improved by reducing the likelihood of influenza exposure from their caregivers. Therefore, the following groups should be vaccinated:

- physicians, nurses, and other personnel in both hospital and outpatient-care settings;
- employees of nursing homes and chronic-care facilities who have contact with patients or residents;
- providers of home care to persons at high risk (e.g., visiting nurses and volunteer workers); and
- household members (including children) of persons in high-risk groups.

VACCINATION OF OTHER GROUPS

Persons Infected with Human Immunodeficiency Virus

Limited information exists regarding the frequency and severity of influenza illness among human immunodeficiency virus (HIV) infected persons, but reports suggest that symptoms might be prolonged and the risk for complications increased for some HIV-infected persons. Influenza vaccine has produced protective antibody titers against influenza in vaccinated HIV-infected persons who have minimal AIDS-related symptoms and high CD4+ T-lymphocyte cell counts. In patients who have advanced HIV disease and low CD4+ T-lymphocyte cell counts, however, influenza vaccine may not induce protective antibody titers; a second dose of vaccine does

Table 1. Influenza vaccine* dosage, by age group, United States, 1998-99 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

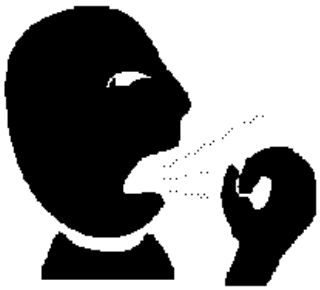
**Contains 15 µg each of A/Beijing/262/95-like (H1N1), A/Sydney/5/97-like (H3N2), and B/Beijing/184/93-like hemagglutinin antigens in each 0.5 mL. For the B/Beijing/184/93-like antigen, U.S. manufacturers will use the antigenically equivalent B/Harbin/07/94 strain because of its growth properties. Manufacturers include Connaught Laboratories, Inc. (Fluzone® whole or split); Evans Medical Ltd. (an affiliate of Medeva Pharmaceuticals, Inc.) (Fluvirin™ purified surface antigen vaccine); Parkedale Pharmaceuticals, Inc. (Fluogen® split); and Wyeth-Ayerst Laboratories (Flushield™ split). For further product information, call Connaught, (800) 822-2463; Evans/Medeva, (800) 234-5535; Parkedale, (800) 358-6436; or Wyeth-Ayerst, (800) 358-7443.*

†Because of their decreased potential for causing febrile reactions, only split-virus vaccines should be used for children. They may be labeled as "split," "subvirion," or "purified-surface-antigen" vaccine. Immunogenicity and side effects of split- and whole-virus vaccines are similar among adults when vaccines are administered at the recommended dosage.

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

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

***Intramuscular.*



not improve the immune response for these persons.

Recent studies have examined the effect of influenza vaccination on replication of HIV type 1 (HIV-1). Although some studies have demonstrated a transient (i.e., 2- to 4-week) increase in replication of HIV-1 in the plasma or peripheral blood mononuclear cells of HIV-infected persons after vaccine administration, other studies using similar laboratory techniques have not indicated any substantial increase in replication. Deterioration of CD4+ T-lymphocyte cell counts and progression of clinical HIV disease have not been demonstrated among HIV-infected persons who receive vaccine. Because influenza can result in serious illness and complications and because influenza vaccination may result in the production of protective antibody titers, vaccination will benefit many HIV-infected patients.

Breast Feeding Mothers

Influenza vaccine does not affect the safety of breast feeding for mothers or infants. Breast feeding does not adversely affect immune response and is not a contraindication for vaccination.

Persons Traveling to Foreign Countries

The risk for exposure to influenza during travel to foreign countries varies, depending on season and destination. In the Tropics, influenza can occur throughout the year; in the Southern Hemisphere, most activity occurs from April through September. Because of the short incubation period for influenza, exposure to the virus during travel can result in clinical illness that begins while traveling, which is an inconvenience or potential danger, especially for persons at increased risk for complications. Persons preparing to travel to the Tropics at any time of year or to the Southern Hemisphere from April through September should review their influenza vaccination histories. If they were not vaccinated the previous fall or winter, they should consider influenza vaccination before travel. Persons in high-risk groups especially should be encouraged to receive the most current vaccine. Persons at high risk who received the previous season's vaccine before travel should be revaccinated in the fall or winter with the current vaccine.

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.

The most frequent side effect of vaccination is soreness at the vaccination site that lasts up to 2 days.

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). Use of amantadine or rimantadine is an option for prevention of influenza A in 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. Specific information about vaccine components can be found in package inserts for each manufacturer.

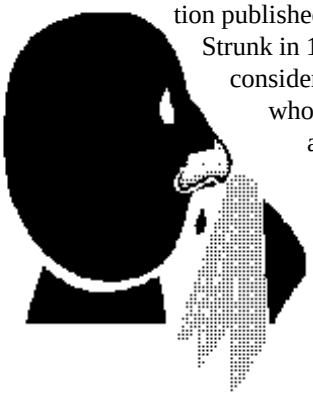
Adults with acute febrile illness usually should not be vaccinated until their symptoms have abated. However, minor illnesses with or without fever should not contraindicate the use of influenza vaccine, particularly among children with mild upper respiratory tract infection or allergic rhinitis.

SIDE EFFECTS AND ADVERSE REACTIONS

Because influenza vaccine contains only noninfectious viruses, it cannot cause influenza. Respiratory disease after vaccination represents coincidental illness unrelated to influenza vaccination. The most frequent side effect of vaccination is soreness at the vaccination site that lasts up to 2 days. These local reactions generally are mild and rarely interfere with the ability to conduct usual daily activities. In addition, two types of systemic reactions have occurred:

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). These reactions begin 6-12 hours after vaccination and can persist for 1 or 2 days. Recent placebo-controlled trials suggest that among elderly persons and healthy young adults, 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.

Immediate, presumably allergic, reactions (e.g., hives, angioedema, allergic asthma, and systemic anaphylaxis) rarely occur after influenza vaccination. 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 due to exposure to egg protein, might also be at increased risk for reactions from influenza vaccine, and similar consultation should be considered. The protocol for influenza vaccination published by Murphy and Strunk in 1985 may be considered for patients who have egg allergies and medical conditions that place them at increased risk for influenza-associated complications.



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 administered as a component of vaccines, even when patch or intradermal tests for thimerosal indicate hypersensitivity. When reported, hypersensitivity to thimerosal usually has consisted of local, delayed-type hypersensitivity reactions.

Although the 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré syndrome (GBS), evidence for a causal relationship of GBS with subsequent vaccines prepared from other virus strains is less clear. However, obtaining strong evidence for a possible small increase in risk is difficult for a rare condition such as GBS, which has an annual background incidence of only 10-20 cases per million adults. During three of four influenza seasons studied from 1977 through 1991, the point estimates of the overall relative risk for GBS after influenza vaccination were slightly elevated but were not statistically significant in any of these studies. However, in a recent study of the 1992-93 and 1993-94 seasons, investigators found an elevation in the overall relative risk for GBS of 1.83 (95% confidence interval=1.12-3.00) during the 6 weeks following vaccination, representing an excess of an estimated 1-2 cases of GBS per million persons vaccinated; the combined number of GBS cases peaked 2 weeks after vaccination. The increase in the relative risk and the increased number of cases in the second week after vaccination may be the result of vaccination but also could be the result of other factors (e.g., confounding or diagnostic bias) rather than a true vaccine-related risk.

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. Even if GBS were a true side effect in subsequent years, the estimated risk for GBS of 1-2 cases per million persons vaccinated is substantially less than that 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. During epidemics from 1972-73 through 1994-95, 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. The potential benefits of influenza vaccination clearly outweigh the possible risks for vaccine-associated GBS.

The average case-fatality ratio for GBS is 6% and increases with age. However, no evidence indicates that the case-fatality ratio for GBS differs among vaccinated persons and those not vaccinated.

Whereas the incidence of GBS in the general population is very low, persons with a history of GBS have a substantially greater likelihood of subsequently developing GBS than persons without such a history. 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 might be causally associated with this risk for recurrence is not known. Avoiding subsequent influenza vaccination of persons known to have developed GBS within 6 weeks of a previous influenza vaccination seems prudent. However, for most persons with a history of GBS who are at high risk for severe complications from influenza, many experts believe 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. 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. 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, including pertussis vaccine (DTaP or DTP). Because influenza vaccine can cause fever when administered to young children, DTaP (which is less frequently associated with fever and other adverse events than is DTP) is preferable.

TIMING OF INFLUENZA VACCINATION ACTIVITIES

Beginning each September (when vaccine for the upcoming influenza season becomes available), persons at high risk who are seen by health-care providers for routine care or as a result of hospitalization should be offered influenza vaccine. Opportunities to vaccinate persons at high risk for complications of influenza should not be missed.

The optimal time for organized vaccination campaigns for persons in high-risk groups is usually the period from October through mid-November. In the United States, influenza activity generally peaks between late December and early March. High levels of influenza activity infrequently occur in the contiguous 48 states before December. Administering vaccine too far in advance of the influenza season should be avoided in facilities such as nursing homes, because antibody levels might begin to decline within a few months of vaccination. Vaccination programs can be undertaken as soon as current vaccine is available if regional influenza activity is expected to begin earlier than December.

Children aged <9 years who have not been vaccinated previously should receive two doses of vaccine at least 1 month apart to maximize the likelihood of a satisfactory antibody response to all three vaccine antigens. The second dose should be administered before December, if possible. Vaccine should be offered to both children and adults up to and even after influenza virus activity is documented in a community.

STRATEGIES FOR IMPLEMENTING INFLUENZA VACCINE RECOMMENDATIONS

Successful vaccination programs have combined education for health-care workers, publicity and education targeted toward potential recipients, a plan for identifying persons at high risk (usually by medical-record review), and efforts to remove administrative and financial barriers that prevent persons from receiving the vaccine. Vaccination pro-

grams should include the patient groups and their caretakers. Persons for whom influenza vaccine is recommended should be identified and vaccinated in settings such as physicians' offices, outpatient clinics, emergency rooms, walk-in clinics, and travelers' clinics, as well as the settings described in the following paragraphs. Persons attended by visiting nurses may be vaccinated in their homes.

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 rather than by obtaining individual vaccination orders for each patient. Consent for vaccination should be obtained from the resident or a family member at the time of admission to the facility, and all residents should be vaccinated at one time, immediately preceding the influenza season. Residents admitted during the winter months after completion of the vaccination program should be vaccinated when they are admitted.

Acute-Care Hospitals

All persons aged ≥65 years and younger persons (including children) with high-risk conditions who are hospitalized at any time from September through March should be offered and strongly encouraged to receive influenza vaccine before they are discharged. Household members and others with whom they will have contact should receive written information about why and where to obtain influenza vaccine.

Outpatient Facilities Providing Continuing Care to Patients at High Risk

All patients should be offered vaccine before the beginning of the influenza season. Patients admitted to such programs (e.g., hemodialysis centers, hospital specialty-care clinics, and outpatient rehabilitation programs) during the winter months after the earlier vaccination program has been conducted should be vaccinated at the time of admission. Household members should receive written information regarding the need for vaccination and the places to obtain influenza vaccine.

Facilities Providing Services to Persons Aged ≥65 Years

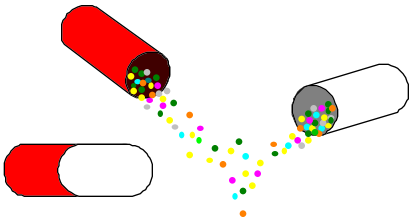
In these facilities (e.g., retirement communities and recreation centers), all unvaccinated residents and attendees should be offered vaccine on site before the influenza season. Education and publicity programs also should be provided; these programs should emphasize the need for influenza vaccine and provide specific information concerning how, where, and when to obtain it.

ANTIVIRAL AGENTS FOR INFLUENZA A

The two antiviral agents with specific activity against influenza A viruses are amantadine hydrochloride and rimantadine hydrochloride. These chemically related drugs interfere with the replication cycle of type A (but not type B) influenza viruses. When administered prophylactically to healthy adults or children before and throughout the epidemic period, both drugs are approximately 70%-90% effective in preventing illness caused by naturally occurring strains of type A influenza viruses. Because antiviral agents taken prophylactically can prevent illness but not subclinical infection, some persons who take these drugs can still develop immune responses that will protect them when they are exposed to antigenically related viruses in later years.

In otherwise healthy adults, amantadine and rimantadine can reduce the severity and duration of signs and symptoms of influenza A illness when administered within 48 hours of illness onset. Studies evaluating the efficacy of treatment for children with either amantadine or rimantadine are limited. Amantadine was approved for treatment and prophylaxis of all influenza type A virus infections in 1976. Although few placebo-controlled studies were conducted to determine the efficacy of amantadine treatment among children before approval, amantadine is indicated for prophylaxis and treatment for adults and children aged ≥1 year. In 1993, rimantadine was approved for treatment and prophylaxis for adults but was approved only for prophylaxis for children. Further studies might provide the data needed to support future approval of rimantadine treatment in this age group.

As with all drugs, amantadine and rimantadine can cause adverse reactions in some persons. Such adverse reactions rarely are severe; however, for some categories of patients, severe adverse reactions are more likely to occur. Amantadine has been associated with a higher incidence of adverse central nervous system (CNS) reactions than rimantadine.



RECOMMENDATIONS FOR THE USE OF AMANTADINE AND RIMANTADINE

Use as Prophylaxis

Chemoprophylaxis is not a substitute for vaccination. Recommendations for chemoprophylaxis are provided primarily to help health-care providers make decisions regarding persons who are at greatest risk for severe illness and complications if infected with influenza A virus.

When amantadine or rimantadine is administered as prophylaxis, factors such as cost, compliance, and potential side effects should be considered when determining the period of prophylaxis. 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.

Persons at High Risk Vaccinated After Influenza A Activity Has Begun

Persons at high risk still can be vaccinated after an outbreak of influenza A has begun in a community. However, the development of antibodies in adults after vaccination can take as long as 2 weeks, during which time chemoprophylaxis should be considered. Children who receive influenza vaccine for the first time can require as long as 6 weeks of prophylaxis (i.e., prophylaxis for 2 weeks after the second dose of vaccine has been received). Amantadine and rimantadine do not interfere with the antibody response to the vaccine.

Persons Providing Care to Those at High Risk

To reduce the spread of virus to persons at high risk, chemoprophylaxis may be considered during community or institutional outbreaks for a) unvaccinated persons who have frequent contact with persons at high risk (e.g., household members, visiting nurses, and volunteer workers) and b) unvaccinated employees of hospitals, clinics, and chronic-care facilities. For those persons who cannot be vaccinated, chemoprophylaxis during the period of peak influenza activity may be considered. For those persons who receive vaccine at a time when influenza A is present in the community, chemoprophylaxis can be administered for 2 weeks after vaccination. Prophylaxis should be considered for all employees, regardless of their vaccination status, if the outbreak is caused by a variant strain of influ-

enza A that might not be controlled by the vaccine.

Persons Who Have Immune Deficiency

Chemoprophylaxis might be indicated for persons at high risk who are expected to have an inadequate antibody response to influenza vaccine. This category includes persons who have HIV infection, especially those who have advanced HIV disease. No data are available concerning possible interactions with other drugs used in the management of patients who have HIV infection. Such patients should be monitored closely if amantadine or rimantadine chemoprophylaxis is administered.

Persons for Whom Influenza Vaccine is Contraindicated

Chemoprophylaxis throughout the influenza season or during peak influenza activity might be appropriate for persons at high risk who should not be vaccinated. Influenza vaccine may be contraindicated in persons who have severe anaphylactic hypersensitivity to egg protein or other vaccine components.

Other Persons

Amantadine or rimantadine also can be administered prophylactically to anyone who wishes to avoid influenza A illness. The health-care provider and patient should make this decision on an individual basis.

Use of Antivirals as Therapy

When administered within 48 hours of illness onset, amantadine and rimantadine can reduce the severity and shorten the duration of influenza A illness among healthy adults. Whether antiviral therapy will prevent complications of influenza type A among persons at high risk is unknown. Insufficient data exist to determine the efficacy of rimantadine treatment among children. Thus, rimantadine is currently approved only for prophylaxis for children, but it is not approved for treatment in this age group.

Amantadine- and rimantadine-resistant influenza A viruses can emerge when either of these drugs is administered for treatment; amantadine-resistant strains are cross-resistant to rimantadine and vice versa. Both the frequency with which resistant viruses emerge and the extent of their transmission are unknown, but data indicate that amantadine- and rimantadine-resistant viruses are no more virulent or transmissible than amantadine- and rimantadine-sensitive viruses.

The screening of naturally occurring epidemic strains of influenza type A has rarely detected amantadine- and rimantadine-resistant viruses. Resistant viruses have most frequently been isolated from persons taking one of these drugs as therapy for influenza A infection. 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. Persons who have influenza-like illness should avoid contact with uninfected persons as much as possible, regardless of whether they are being treated with amantadine or rimantadine. Persons who have influenza type A infection and who are treated with either drug can shed amantadine- or rimantadine-sensitive viruses early in the course of treatment, but can later shed drug-resistant viruses, especially after 5-7 days of therapy. Such persons can benefit from therapy even when resistant viruses emerge; however, they also can transmit infection to other persons with whom they come in contact. Because of possible induction of amantadine or rimantadine resistance, treatment of persons who have 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. Laboratory isolation of influenza viruses obtained from persons who are receiving amantadine or rimantadine should be reported to CDC through state health departments, and the isolates should be sent to CDC for antiviral sensitivity testing.

Outbreak Control in Institutions

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. Contingency planning is needed to ensure rapid administration of amantadine or rimantadine to residents. This planning should include pre-approved medication orders or plans to obtain physicians' orders on short notice. When amantadine or rimantadine is used for outbreak control, the drug should be administered to all residents of the institution, regardless of whether they received influenza vaccine the previous fall. The drug should be continued for at least 2 weeks or until approximately 1 week after the end of the outbreak. The dosage for each resident should be determined after consulting the dosage recommendations and precautions and the manufacturer's package insert. To reduce the spread of virus and to minimize disruption of patient care, 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 controlled by the vaccine.

Chemoprophylaxis also may be considered for controlling influenza A outbreaks in other closed or semi-closed settings (e.g., dormitories or other settings where persons live in close proximity). To reduce the spread of infection and the chances of prophylaxis failure resulting from transmission of drug-resistant virus, measures should be taken to reduce contact as much as possible between persons on chemoprophylaxis and those taking drug for treatment.

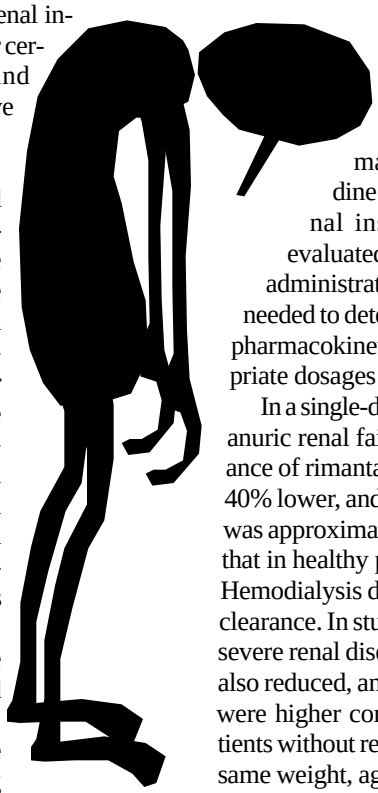
CONSIDERATIONS FOR SELECTING AMANTADINE OR RIMANTADINE FOR CHEMOPROPHYLAXIS OR TREATMENT

Side Effects and Toxicity

Despite the similarities between the two drugs, amantadine and rimantadine differ in

their pharmacokinetic properties. More than 90% of amantadine is excreted unchanged, whereas approximately 75% of rimantadine is metabolized by the liver. However, both drugs and their metabolites are excreted by the kidneys.

The pharmacokinetic differences between amantadine and rimantadine might explain differences in side effects. Although both drugs can cause CNS and gastrointestinal side effects when administered to young, healthy adults at equivalent dosages of 200 mg/day, the incidence of CNS side effects (e.g., nervousness, anxiety, difficulty concentrating, and light-headedness) is higher among persons taking amantadine compared with those taking rimantadine. In a 6-week study of prophylaxis in healthy adults, approximately 6% of participants taking rimantadine at a dosage of 200 mg/day experienced at least one CNS symptom, compared with approximately 14% of those taking the same dosage of amantadine and 4% of those taking placebo. Gastrointestinal side effects (e.g., nausea and anorexia) occur in approximately 3% of persons taking either drug, compared with 1%-2% of persons receiving the placebo. Side effects associated with both drugs are usually mild and cease soon after discontinuing the drug. Side effects can diminish or disappear after the first week despite continued drug ingestion. However, serious side effects have been observed (e.g., marked behavioral changes, delirium, hallucinations, agitation, and seizures). 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. Clinical observations and studies have indicated that lowering the dosage of amantadine among these persons reduces the incidence and severity of such side effects, and recommendations for reduced dosages for these groups of patients have been made. Because rimantadine has been marketed for a shorter period of time than amantadine, its safety in certain patient populations (e.g., chronically ill and elderly persons) has been evaluated less frequently. Clinical trials of rimantadine have more commonly involved young, healthy persons.



Providers should review the package insert before using amantadine or rimantadine for any patient. The patient's age, weight, and renal function; the presence of other medical conditions; the indications for use of amantadine or rimantadine (i.e., prophylaxis or therapy); and the potential for interaction with other medications must be considered, and the dosage and duration of treatment must be adjusted appropriately. Modifications in dosage might be required for persons who have impaired renal or hepatic function, the elderly, children, and persons with a history of seizures (Table 2). The following are guidelines for the use of amantadine and rimantadine in certain patient populations.

Persons Who Have Impaired Renal Function

Amantadine

Amantadine is excreted unchanged in the urine by glomerular filtration and tubular secretion. Thus, renal clearance of amantadine is reduced substantially in persons with renal insufficiency. 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. However, 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 so that adverse reactions can be recognized promptly and either the dose can be further reduced or the drug can be discontinued, if necessary. Hemodialysis contributes minimally to drug clearance.

Rimantadine

The safety and pharmacokinetics of rimantadine among patients with renal insufficiency have been evaluated only after single-dose administration. Further studies are needed to determine the multiple-dose pharmacokinetics and the most appropriate dosages for these patients.

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. 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 compared with control patients without renal disease who were the same weight, age, and sex.

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.

Persons Aged ≥65 Years

Amantadine

Because renal function declines with increasing age, the daily dose for persons aged ≥65 years should not exceed 100 mg for prophylaxis or treatment. For some elderly persons, the dose should be further reduced. Studies suggest that because of their smaller average body size, elderly women are more likely than elderly men to experience side effects at a daily dose of 100 mg.

Rimantadine

The incidence and severity of CNS side effects among elderly persons appear to be substantially lower among those taking rimantadine at a dosage of 200 mg/day compared with elderly persons taking the same dosage of amantadine. However, when rimantadine has been administered at a dosage of 200 mg/day to chronically ill elderly persons, they have had a higher incidence of CNS and gastrointestinal symptoms than healthy, younger persons taking rimantadine at the same dosage. After long-term administration of rimantadine at a dosage of 200 mg/day, serum rimantadine concentrations among elderly nursing-home residents have been twofold to fourfold greater than those reported among younger adults.

The dosage of rimantadine should be reduced to 100 mg/day for prophylaxis or treatment for elderly nursing-home residents. Although further studies are needed to determine the optimal dosage for other elderly persons, a reduction in dosage to 100 mg/day should be considered for all persons aged ≥65 years if they experience signs and symptoms that might represent side effects when taking a dosage of 200 mg/day.

Persons Who Have Liver Disease

Amantadine

No increase in adverse reactions to amantadine has been observed among persons who have 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.

Rimantadine

The safety and pharmacokinetics of rimantadine among persons who have liver disease have been evaluated only after single-dose administration. In a study of persons with chronic liver disease (most with stabilized cirrhosis), no alterations were observed after a single dose. However, for persons with severe liver dysfunction, the apparent clearance of rimantadine was 50% lower than that reported for persons without liver disease. A dosage reduction to 100 mg/day is recommended for persons with severe hepatic dysfunction.

Persons Who Have Seizure Disorders

Amantadine

An increased incidence of seizures has been reported in patients with a history of seizure disorders who have received amantadine. 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. The extent to which rimantadine might increase the incidence of seizures among persons with seizure disorders has not been adequately evaluated.

Children

Amantadine

The use of amantadine among children aged <1 year has not been adequately evaluated. The Food and Drug Administration-approved dosage for children aged 1-9 years is 4.4-8.8 mg/kg/day, not to exceed 150 mg/day. Although further studies to determine the optimal dosage for children are needed, 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; however, for children weighing <40 kg, prescribing 5 mg/kg/day, regardless of age, is advisable.

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, also is recommended.

Table 2. Recommended daily dosage for amantadine and rimantadine treatment and prophylaxis

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

Note: Amantadine manufacturers include Dupont Pharma (Symmetrel®, syrup); Chase Pharmaceuticals, Invamed, and Endo Pharmaceuticals (Amantadine HCL, capsule); and Copley Pharmaceuticals, Barre National, and Mikart (Amantadine HCL, syrup). Rimantadine is manufacturered by Forest Laboratories (Flumadine®, tablet and syrup).

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

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

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

***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.*

NA = Not applicable.

Drug Interactions

Amantadine

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 may increase the incidence of adverse CNS reactions.

Rimantadine

No clinically significant interactions between rimantadine and other drugs have been identified. For more detailed information concerning potential drug interactions for either drug, the package insert should be consulted.

SOURCES OF INFORMATION ON INFLUENZA-CONTROL PROGRAMS

Information regarding influenza surveillance is available through the CDC Voice Information System (influenza update), (888) 232-3228; through the CDC Fox Information Service, (888) 232-3299; or through the CDC Influenza Branch's World-Wide Web site 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, and information about state or local influenza activity.

Cases of Selected Notifiable Diseases Reported in Virginia*

Disease	Total Cases Reported, July 1998						Total Cases Reported Statewide, January through July		
	State	Regions					This Year	Last Year	5 Yr Avg
		NW	N	SW	C	E			
AIDS	61	5	11	8	15	22	492	675	770
Campylobacteriosis	85	27	18	13	20	7	348	303	365
Giardiasis	21	5	8	2	1	5	188	230	164
Gonorrhea	1024	39	125	92	251	517	3953	4614	6062
Hepatitis A	11	0	7	1	0	3	137	118	99
Hepatitis B	3	0	0	1	1	1	56	76	76
Hepatitis NANB	2	0	0	0	0	2	7	18	15
HIV Infection	47	0	12	6	15	14	497	560	530
Influenza	0	0	0	0	0	0	1034	438	627
Legionellosis	1	0	0	1	0	0	8	12	8
Lyme Disease	11	1	5	1	2	2	31	16	28
Measles	0	0	0	0	0	0	2	1	1
Meningitis, Aseptic	8	1	3	2	1	1	69	100	120
Meningitis, Bacterial†	2	2	0	0	0	0	31	50	57
Meningococcal Infections	1	0	1	0	0	0	24	37	38
Mumps	1	0	0	0	0	1	5	7	15
Pertussis	1	1	0	0	0	0	7	32	22
Rabies in Animals	27	7	3	6	5	6	357	349	272
Rocky Mountain Spotted Fever	4	0	3	1	0	0	6	7	9
Rubella	0	0	0	0	0	0	0	1	1
Salmonellosis	132	18	33	21	32	28	518	471	517
Shigellosis	17	2	4	3	3	5	83	283	310
Syphilis, Early‡	25	2	2	3	5	13	263	375	637
Tuberculosis	26	2	11	2	5	6	174	194	202

Localities Reporting Animal Rabies This Month: Albemarle 2 raccoons; Fairfax 1 groundhog, 1 raccoon; Franklin County 1 fox; Hanover 1 skunk; Henrico 1 bat, 1 fox; King & Queen 1 raccoon; Loudoun 1 raccoon; Madison 1 raccoon; Montgomery 1 raccoon; New Kent 1 raccoon; Page 1 fox; Pittsylvania 2 raccoons; Pulaski 1 raccoon; Rockbridge 1 raccoon; Russell 1 raccoon; Spotsylvania 1 raccoon; Stafford 1 fox; Suffolk 2 raccoons; Surry 1 fox; Virginia Beach 1 bat, 1 raccoon; Williamsburg 1 raccoon.

Occupational Illnesses: Arsenic exposure 1; Asbestosis 18; Carpal Tunnel Syndrome 42; DeQuervains Syndrome 1; Hearing Loss 14; Lead exposure 1; Pneumoconiosis 4.

*Data for 1998 are provisional. †Other than meningococcal. ‡Includes primary, secondary, and early latent.

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