VIRGINIA
EPIDEMIOLOGY BULLETIN

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August 1999 Volume 99, No. 8

Prevention and Control of Influenza:

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

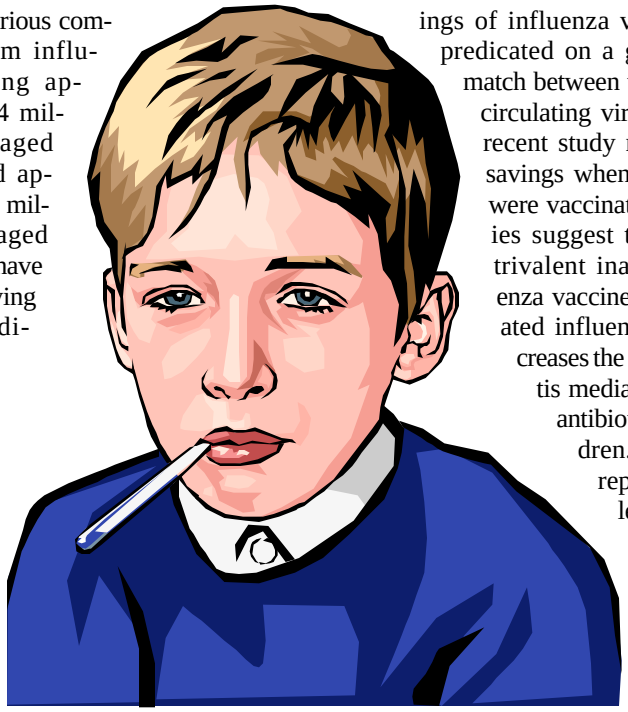
Summary

The following article is adapted from the MMWR article with the above title (1999;48[No. RR-4]:1-28). This report updates 1998 recommendations by the Advisory Committee on Immunization Practices on the use of influenza vaccine and antiviral agents. The principal changes include a) information on the influenza virus strains included in the 1999-2000 trivalent vaccine; b) discussion of the potential expanded use of influenza vaccine; c) new background information on live-attenuated influenza vaccines, neuraminidase-inhibitor drugs, and rapid diagnostic tests; and d) new information on the epidemiology of influenza among travelers. This report and other information on influenza can be accessed at the Centers for Disease Control and Prevention website 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. Influenza viruses also can cause global epidemics of disease, known as pandemics, during which rates of morbidity and mortality from influenza-related complications can increase dramatically. Influenza viruses cause disease in all age groups. Rates of infection are highest among children, but rates of serious morbidity and mortality 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.

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 the influenza vaccination recommendations includes persons who are at high risk for serious complications from influenza, including approximately 34 million persons aged ≥65 years and approximately 32 million persons aged <65 years who have chronic underlying medical conditions.



Increases in Vaccination Coverage Levels

Among persons aged ≥65 years, influenza vaccination levels have increased from 33% in 1989 to 65.5% in 1997. The 1997 vaccination coverage level surpassed the Healthy People 2000 goal of 60%. Although influenza vaccination coverage increased in black, Hispanic, and white populations, coverage levels among blacks and Hispanics continue to lag behind levels among whites. 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.

The cost-effectiveness and cost savings of influenza vaccination are predicated on a good antigenic match between the vaccine and circulating virus strains. One recent study reported a cost savings when healthy adults were vaccinated. 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. Despite these reported benefits, less than 30% of persons who are aged <65 years and at high risk for influenza-related complications are vaccinated each year. Increasing vaccination coverage among these high-risk groups now is the highest priority for expanding influenza vaccine use.

Influenza and Its Burden

Biology of Influenza

Influenza A and B are the two types of influenza viruses that cause epidemic human

disease. Influenza A viruses are further classified into subtypes on the basis of two surface antigens: hemagglutinin (H) and neuraminidase (N). Although both influenza A and B viruses undergo continual antigenic change (i.e., antigenic drift), influenza B viruses undergo antigenic drift less rapidly and are not divided into subtypes. 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 the severity of disease if infection occurs. However, antibody against one influenza virus type or subtype confers little or no protection against another virus type or subtype. Furthermore, antibody to one strain of influenza virus might not protect against a distantly related strain of the same subtype. The constant 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 virus strains in each year's influenza vaccine.

Clinical Signs and Symptoms of Influenza

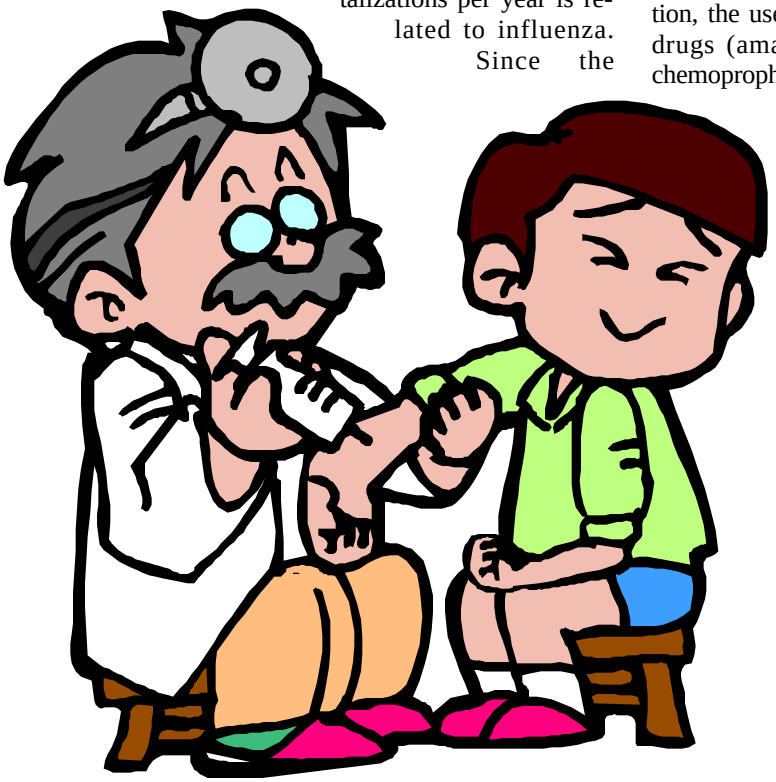
Uncomplicated influenza illness is characterized by the abrupt onset of constitutional and respiratory signs and symptoms (e.g., fever, myalgia, headache, severe malaise, sore throat, rhinitis, and nonproductive cough). Illness typically resolves after several days for most persons, although cough and 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.

Hospitalizations and Deaths from Influenza

The risks for complications, hospitalization, and death from influenza are higher among persons aged ≥65 years and persons of any age with some underlying health conditions than among healthy children and adults. Estimated rates of influenza-associated hospitalizations have varied substantially in studies of different influenza epidemics occurring from 1972 through 1981:

- 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.
- Among children aged 5-14 years, rates have ranged from approximately 200 per 100,000 population for those with high-risk conditions to 20 per 100,000 population for those without high-risk conditions.
- Among persons aged 15-44 years, rates have ranged from approximately 40 to 60 per 100,000 population for those with high-risk conditions and from approximately 20 to 30 per 100,000 population for those without high-risk conditions.
- Among persons aged 45-64 years, rates have ranged from approximately 80 to 400 per 100,000 population for those with high-risk medical conditions and from approximately 20 to 40 per 100,000 population for those without high-risk conditions.
- Among persons aged ≥65 years, rates have ranged from approximately 200 to greater than 1,000 per 100,000 population.

During influenza epidemics from 1969-1970 through 1993-1994, the estimated number of influenza-associated hospitalizations in the United States has ranged from approximately 20,000 to greater than 300,000 per epidemic. A review of national data indicates an average of approximately 110,000 hospitalizations per year is 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 148,000 influenza-associated hospitalizations each year.



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. During those 19 influenza seasons, estimated rates of influenza-associated death ranged from approximately 25 to >150 deaths per 100,000 persons aged ≥65 years. These older adults account for approximately 90% of the deaths attributed to pneumonia and influenza. From 1972-1973 through 1994-1995, an estimated >20,000 influenza-associated deaths occurred during each of 11 different U.S. epidemics, and >40,000 influenza-associated deaths occurred during each of six of these 11 epidemics. In the United States, pneumonia and influenza deaths might be increasing in part because the number of elderly persons is increasing.

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 (amantadine or rimantadine) for chemoprophylaxis or therapy of influenza A infection is an important adjunct to vaccine (see Recommendations for the Use of Antiviral Agents for Influenza A).

Influenza Vaccine

Vaccinating persons at high risk for complications before the influenza season each year is the most effective means of reducing the impact of influenza. Vaccination coverage can be increased by administering vaccine to persons during hospitalizations or routine health-care visits before the influenza season, making special visits to physicians' offices or clinics unnecessary. When vaccine and epidemic strains of virus are well matched, achieving high vaccination rates among persons liv-

ing in closed settings (e.g., nursing homes and other chronic-care facilities) and among the staff can reduce the risk for outbreaks by inducing herd immunity.

Effectiveness of Inactivated Influenza Vaccine

Influenza vaccine now contains three virus strains (usually 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 (inactivated). 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. Elderly persons and persons with certain chronic diseases might develop lower post-vaccination antibody titers than healthy young adults and thus can remain susceptible to influenza-related upper respiratory tract infection. However, among such persons, the vaccine can be effective in preventing secondary complications and reducing the risk for hospitalization and death.

The effectiveness of influenza vaccine depends primarily on the age and immunocompetence of the vaccine recipient and the degree of similarity between the virus strains 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 younger than age 65 years. Among elderly persons living outside nursing homes or similar chronic-care facilities, influenza vaccine is 30%-70% effective in preventing hospitalization for pneumonia and influenza. 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%.

Influenza Strains Contained in the 1999-2000 Vaccine

The trivalent influenza vaccine prepared for the 1999-2000 season will include A/Beijing/262/95-like (H1N1), 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 B/Yamanashi/166/98 virus because of its growth properties and because it is representative of currently circulating B viruses.

Antiviral Agents

In the United States, two antiviral agents are licensed for use in preventing and treating influenza A: amantadine hydrochloride and rimantadine hydrochloride. These antiviral drugs are an important adjunct to influenza vaccine. As a prophylaxis, these

agents are appropriate for persons who are at high risk of influenza complications and who are vaccinated after influenza activity has begun; persons who provide care to those at high risk; persons with immune deficiency; and some persons who are at high risk but who cannot be vaccinated. Moreover, these agents can prevent influenza illness while allowing subclinical infection, thus allowing some persons to develop protective immune responses to circulating influenza viruses. As a treatment, both amantadine and rimantadine can shorten the duration of influenza A illness among healthy adults and children.

Recommendations for the Use of Influenza Vaccine

Influenza vaccine is strongly recommended for any person ≥6 months who, because of age or underlying medical condition, is at increased risk for complications of influenza. In addition, health-care workers and others (including household members) in close contact with persons in high-risk groups should be vaccinated to decrease the risk of transmitting infection to persons at high risk. Influenza vaccine also can 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).

Target Groups for Vaccination

Persons at High Risk for Influenza-Related Complications

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

- persons aged ≥65 years;
- residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions;
- adults and children who have chronic disorders of the pulmonary or cardiovascular systems, including asthma;
- adults and children who have required regular medical follow-up or hospitalization during the preceding year because of chronic metabolic diseases (including diabetes mellitus), renal dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications);
- 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; and
- women who will be in the second or third trimester of pregnancy during the influenza season.

Influenza-associated excess mortality among pregnant women was documented during the pandemics of 1918-1919 and 1957-1958. 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. 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. Women in their third trimester of pregnancy were hospitalized at a rate (250 per 100,000 pregnant women) comparable to that of nonpregnant women with high-risk medical conditions. Using data from this study, researchers estimated that an average of 1-2 hospi-

talizations 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 more than 2,000 pregnant women demonstrated no adverse fetal effects associated with influenza vaccine. However, more data are needed to confirm the safety of vaccination during pregnancy. Some experts prefer to administer influenza vaccination during the second trimester to avoid a coincidental association with spontaneous abortion, which is common in the first trimester, and because exposures to vaccines have traditionally been avoided during the first trimester.

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. Efforts to protect members of high-risk groups against influenza might be improved by reducing the likelihood of influenza exposure from their care givers. 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;
- employees of assisted living and other residences for persons in high-risk groups;
- persons who provide home care to persons in high-risk groups; and
- household members (including children) of persons in high-risk groups.

Other Groups To Consider

Persons Infected with Human Immunodeficiency Virus

Limited information exists regarding the frequency and severity of influenza illness or the benefits of influenza vaccination among persons with human immunodeficiency virus (HIV) infection. 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. Other reports suggest that influenza symptoms might be prolonged and the risk for complications from influenza increased for some HIV-infected persons.

Influenza vaccine has produced 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. However, in patients who have advanced HIV disease and low CD4+ T-lymphocyte cell counts, influenza vaccine might not induce protective antibody titers; a second dose of vaccine does not improve the immune response in these persons.

One study found that HIV RNA levels increased transiently in one HIV-infected patient after influenza infection. 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 documented a substantial increase in the replication of HIV. Deterioration of CD4+ T-lymphocyte cell counts and progression of HIV disease have not been demonstrated among HIV-infected persons who receive vaccine. The effect of antiretroviral therapy on potential increases in HIV RNA levels following either natural influenza infection or influenza vaccination is unknown. 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 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, whereas most influenza activity occurs from April through September in the temperate regions of the Southern Hemisphere. 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 containing persons from areas of the world where influenza viruses are circulating.

Persons at high risk for complications of influenza should consider receiving influenza vaccine before travel if they were not vaccinated with influenza vaccine during the preceding fall or winter and they plan to a) travel to the tropics; b) travel with large organized tourist groups at any time of year; or c) travel to the Southern Hemisphere from April through September. 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.

Because influenza vaccine might not be available during the summer in North America, persons aged ≥65 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 advisability of carrying antiviral medications for either prophylaxis or treatment for 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). Use of an antiviral agent (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.

Administration of Influenza Vaccine

Timing

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 as a result of hospitalization. For organized vaccination campaigns, the optimal time to vaccinate persons in high-risk groups is usually from October through mid-November, because influenza activity in the United States generally peaks between late December and early March. Administering vaccine too far in advance of the influenza season should be avoided in facilities such as nursing homes, because antibody levels can begin to decline within a few months of vaccination. If regional influenza activity is expected to begin earlier than December, vaccination programs can be undertaken as soon as current vaccine is available. Vaccine should be offered to unvaccinated persons even after influenza virus activity is documented in a community.

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.

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. 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, 1999-2000 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/Yamanashi/166/98 strain because of its growth properties. Manufacturers include Connaught Laboratories, Inc. (Fluzone® whole or split); Medeva Pharma Ltd. (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; 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.*

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.

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) respiratory disease after vaccination is coincidental and unrelated to influenza 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. 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). 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, 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 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.

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.

Guillain-Barré Syndrome

The 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré syndrome (GBS). 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 virus strains 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, 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. 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. 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. Good evidence exists that several infectious illnesses, most notably *Campylobacter jejuni* as well as upper respiratory tract infections in general, are associated with GBS.

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. 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. The potential benefits of influenza vaccination in preventing serious illness, hospitalization, and death greatly outweigh the possible risks for developing vaccine-associated GBS.

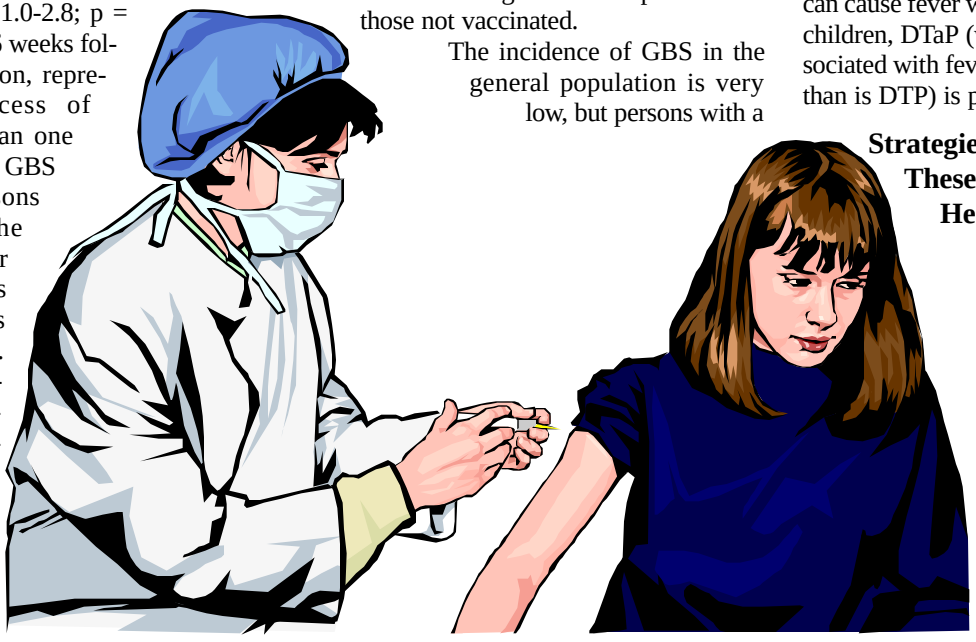
The average case-fatality ratio for GBS is 6% and increases with age. However, no evidence indicates that the case-fatality ratio for GBS differs among vaccinated persons and those not vaccinated.

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. 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 influenza vaccination of persons who are not at high risk for severe influenza complications and who are known to have developed GBS within 6 weeks of 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. 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.



Strategies for Implementing These Recommendations in Health-Care Settings

Successful vaccination programs combine 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 re-

ceiving the vaccine. 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 in high-risk groups 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 in high-risk groups 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, immediately 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

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.

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

Nursing-care plans should identify patients in high-risk groups, 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 ≥65 Years

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

Other 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. 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. LAIVs consist of live virus strains that induce minimal symptoms (i.e., attenuated) and that replicate poorly at temperatures found in the lower respiratory tract (i.e., temperature sensitive). The potential advantages of LAIVs are their ability 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 LAIV (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. 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%. 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. No study has directly compared the effectiveness or efficacy of trivalent inactivated vaccine and trivalent LAIV.

Potential Expansion of 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. These discussions were started because a) the impact of influenza might decline because of the development and potential combined use of new influenza vaccines, antiviral agents, and commercial rapid detection kits; b) the risk of influenza-related hospitalizations might be substantially increased among healthy children aged <5 years compared with older children; and c) a substantial cost benefit might

result from vaccinating groups such as healthy young adults, who traditionally are not considered to be at high risk for influenza-related complications.

Young Children

Several studies indicate that rates of hospitalizations are higher among young children than older children when influenza viruses are in circulation. The increased rates for hospitalizations 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 morbidity among children and which frequently circulate during the same time as influenza viruses. Recent unpublished studies have been undertaken to separate the effects of respiratory syncytial viruses and influenza viruses on rates of hospitalizations among children aged <5 years who do not have high-risk conditions. If these and other studies indicate that the risk of hospitalizations from influenza is increased among young and healthy children, then the ACIP will consider extending vaccine recommendations to this group after the logistic and economic consequences of such a recommendation are adequately addressed.

Adults Aged 50-64 Years

Rates of influenza-related hospitalizations and mortality among persons aged 50-64 years suggest that this group might be at increased risk for influenza-related complications. The prevalence of chronic medical conditions is higher in this group than among younger adults. However, further studies of this age group are needed to clarify the risks for complications from influenza and to document the potential impact of recommending routine influenza vaccination for this group.

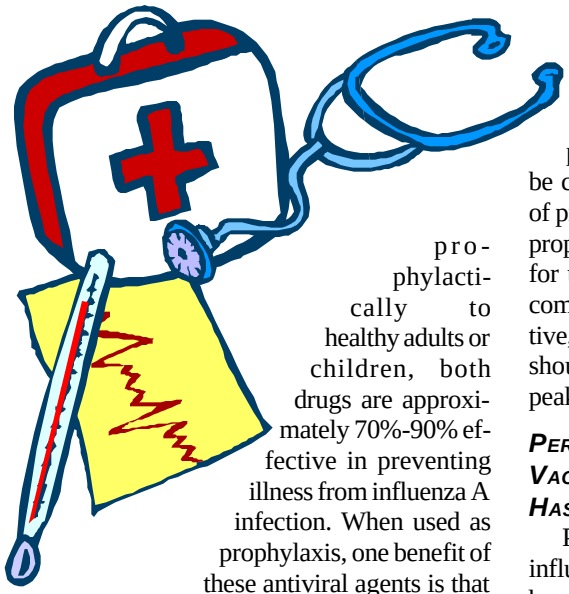
Recommendations for the Use of Antiviral Agents for Influenza A

Antiviral drugs for influenza are an important adjunct to influenza vaccine for the control and prevention of influenza. The currently licensed agents are amantadine hydrochloride and rimantadine hydrochloride, which are chemically related antiviral drugs with specific activity against influenza A viruses but not influenza B viruses. Amantadine was 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. Another class of antiviral agents with activity against both influenza A and B viruses is under development and testing (see Evolving Developments Related to Influenza Antiviral Agents).

Amantadine and rimantadine differ in terms of pharmacokinetics, side effects, and costs. In particular, rimantadine is associated with fewer central nervous system side effects than amantadine, but it is more expensive.

Indications for Use

Amantadine and rimantadine are indicated for the prophylaxis and treatment of influenza A infection. When administered



prophylactically to healthy adults or children, both drugs are approximately 70%-90% effective in preventing illness from influenza A infection. When used as prophylaxis, one benefit of these antiviral agents is that they can prevent illness while permitting subclinical infection. Therefore, some persons who take these drugs will develop protective immune responses to circulating influenza viruses. When administered as treatment within 48 hours of illness onset in healthy adults, amantadine and rimantadine can reduce the severity and duration of signs and symptoms of influenza A illness. Studies of the efficacy of either amantadine or rimantadine treatment in children are limited.

Role of Viral Diagnosis

The appropriate treatment of patients with viral respiratory illness depends on accurate and timely diagnosis. The early diagnosis of influenza also can help reduce the inappropriate use of antibiotics, a growing major public health problem. Currently, several commercial assays are available that can be used in a clinic setting to rapidly (30 minutes or less) detect influenza viruses, and additional commercial assays are available for use by laboratories. No published study has directly compared the sensitivity, specificity, positive predictive value, and negative predictive value of these assays for detecting influenza in clinical specimens.

The use of viral culture, in addition to rapid diagnostic tests, remains critical, because only cultures yield viruses that can be characterized to provide specific information on circulating influenza subtypes and strains. This information is needed to assess the match between current circulating and vaccine strains and to help formulate vaccine for the coming year.

Administration of Amantadine and Rimantadine

Use for Prophylaxis

Chemoprophylaxis is not a substitute for vaccination. When amantadine or rimantadine is administered as prophylaxis, factors related to 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 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 A has begun in a community. However, the development of antibodies in adults after vaccination can take as long as 2 weeks. In this situation, chemoprophylaxis should be considered for such persons 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 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 Who Provide Care to Those at High Risk

During community or institutional outbreaks, chemoprophylaxis during peak influenza activity can be considered for unvaccinated persons who have frequent contact with persons at high risk to reduce the spread of virus to persons at high risk. Persons with frequent contact include household members, visiting nurses, volunteer workers, and em-

ployees of hospitals, clinics, and chronic-care facilities. If the 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 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.

Use for Treatment

Amantadine and rimantadine can reduce the severity and shorten the duration of influenza A illness among healthy adults when administered within 48 hours of illness onset. Whether antiviral therapy will prevent complications of influenza type A among persons at high risk is unknown. Among children, rimantadine is approved for prophylaxis only, although many experts believe rimantadine is also appropriate for therapy.

To reduce the emergence of antiviral drug-resistant viruses, 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.

Use for the Control of Influenza Outbreaks in Institutions

Most published reports on the use of antiviral drugs to control institutional outbreaks of influenza 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 continued for at least 2 weeks or until approximately 1 week after the end of the outbreak. The individual dosage for each resident should be determined. 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 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).

Whenever any institutional outbreak occurs, 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, to limit the potential transmission of drug-resistant virus.

Dosage

Dosage recommendations vary by age group (Table 2).

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

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 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 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/1.73m².*

†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.

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.

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. However, chronically ill elderly persons have had a higher incidence of CNS and gastrointestinal symptoms and twofold to fourfold higher serum concentrations than healthy, younger persons when rimantadine has been administered at a dosage of 200 mg/day.

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 ≥65 years who experience side effects when taking a dosage of 200 mg/day.

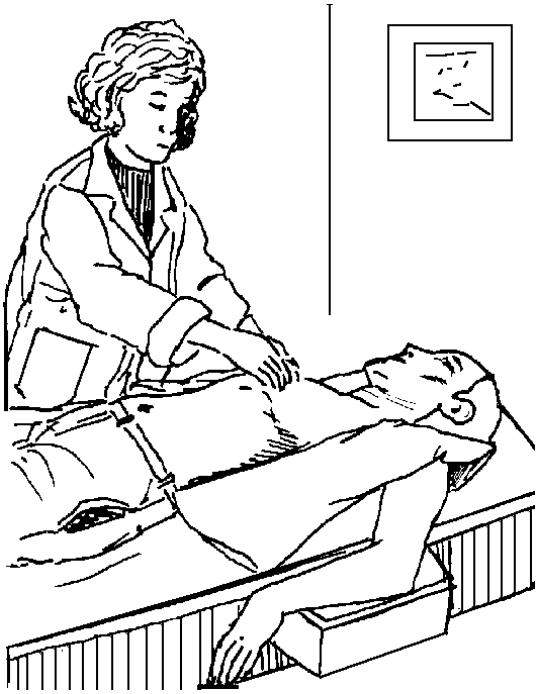
Persons With Impaired Renal Function

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.

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.

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.



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

Route

Amantadine and rimantadine are administered orally. Both antiviral drugs are available in tablet or syrup form.

Pharmacokinetics

Despite their similarities, amantadine and rimantadine differ substantially in their pharmacokinetic properties. More than 90% of 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, and dosages might need to be decreased.

Approximately 75% of rimantadine is metabolized by the liver. The safety and pharmacokinetics of rimantadine among persons with 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 in liver function were observed after a single dose. However, for persons with severe liver dysfunction, the apparent clearance of rimantadine was 50% lower than that reported for persons without liver disease.

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. 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. 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.

Side Effects and Adverse Reactions

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. 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. 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.

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 (Table 2). 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.

The patient's age, weight, and renal function; 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 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, persons aged ≥65 years, children, and persons with a history of seizures (Table 2).

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.

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

Antiviral Drug-Resistant Strains of Influenza

Amantadine-resistant viruses are cross-resistant to rimantadine and vice versa. Drug-resistant viruses can appear in up to approximately one third of patients when either amantadine or rimantadine is used for therapy. During the course of therapy, antiviral-resistant influenza strains can replace sensitive strains within 2-3 days of starting therapy. 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; 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 no more virulent or transmissible than sensitive viruses. The screening of epidemic strains of influenza A has rarely detected amantadine- and rimantadine-resistant viruses.

Persons who have influenza A infection and who are treated with either drug can shed sensitive viruses early in the course of treatment and later shed drug-resistant viruses, especially after 5-7 days of therapy. Such persons can benefit from therapy even when resistant viruses emerge. Influenza isolates 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.

Evolving Developments Related to Antiviral Agents for Influenza

The currently available antiviral drugs rimantadine and amantadine are effective only for influenza A viruses. Another class of influenza antiviral drugs, neuraminidase inhibitors, which selectively inhibit both influenza A and B viruses, is under development and testing. Neuraminidase inhibitors are sialic acid analogues. Recent studies have found neuraminidase inhibitors to be 67%-82% effective in preventing laboratory-confirmed infection when administered as prophylaxis and to reduce the duration of illness by 1-1.5 days when started within 36-48 hours of illness onset. The reported adverse effects of these drugs are substantially different from amantadine and rimantadine; in particular, the drugs do not appear to affect the central nervous system. The intranasal spray/inhalation form of the drugs has been licensed by the U.S. Food and Drug Administration and should be available in October 1999.

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 their control.

Cases of Selected Notifiable Diseases Reported in Virginia*

Disease	Total Cases Reported, July 1999: State	Regions: NW	N	SW	C	E	Total Cases Reported Statewide, January through July: This Year	Last Year	5 Yr Avg
AIDS	96	3	40	4	19	30	462	494	660
Campylobacteriosis	109	30	21	8	22	28	367	348	358
***E. coli* O157:H7**	10	4	1	2	0	3	35	35	28
Giardiasis	50	13	18	5	7	7	199	188	172
Gonorrhea	862	74	69	131	234	354	5602	3971	5542
Hepatitis A	21	3	10	0	4	4	97	137	108
B, acute	10	0	0	0	4	6	59	56	70
C/NANB, acute	0	0	0	0	0	0	10	7	12
HIV Infection	63	0	24	2	17	20	436	493	586
Lead in Children†	42	4	6	9	12	11	197	292	367
Legionellosis	3	1	0	2	0	0	16	8	9
Lyme Disease	30	8	13	3	2	4	48	31	28
Measles	0	0	0	0	0	0	3	2	1
Meningococcal Infection	6	2	2	0	1	1	32	24	37
Mumps	0	0	0	0	0	0	8	5	13
Pertussis	0	0	0	0	0	0	13	7	18
Rabies in Animals	55	18	20	4	11	2	304	357	301
Rocky Mountain Spotted Fever	7	5	1	1	0	0	8	6	9
Rubella	0	0	0	0	0	0	0	0	1
Salmonellosis	174	29	24	23	64	34	663	518	523
Shigellosis	20	0	8	10	1	1	58	83	253
Syphilis, Early§	21	0	4	8	3	6	224	262	536
Tuberculosis	18	2	2	1	0	13	149	173	190

Localities Reporting Animal Rabies This Month: Accomack 1 dog; Amelia 1 raccoon; Buckingham 1 raccoon; Campbell 1 raccoon; Charles City 1 raccoon; Chesterfield 1 bat, 1 raccoon; Clarke 1 skunk; Essex 1 cat; Fairfax 6 bats, 4 foxes, 5 raccoons, 1 skunk; Fauquier 1 fox, 1 raccoon; Floyd 1 raccoon; Fluvanna 1 cat; Frederick 1 raccoon; Greensville 1 skunk; Halifax 1 skunk; Hanover 1 skunk; King George 2 raccoons; Loudoun 1 fox, 1 raccoon; Nelson 1 raccoon, 1 skunk; Nottoway 2 skunks; Orange 1 raccoon; Page 1 raccoon, 2 skunks; Prince William 1 groundhog, 1 raccoon; Pulaski 1 cat, 1 raccoon; Richmond City 1 raccoon; Rockingham 2 raccoons; Spotsylvania 2 raccoons; Stafford 1 cat.

Occupational Illnesses: Asbestosis 19; Lead Exposure 6; Mercury Exposure 1; Pneumoconiosis 6.

*Data for 1999 are provisional. †Elevated blood lead levels ≥10µg/dL.

§Includes primary, secondary, and early latent.

Published monthly by the
VIRGINIA DEPARTMENT OF HEALTH
Office of Epidemiology
P.O. Box 2448
Richmond, Virginia 23218
http://www.vdh.state.va.us
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