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Prevention and Control of Influenza

Recommendations of the Advisory Committee on Immunization Practices (ACIP)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Prevention and Control of Influenza Recommendations of the Advisory Committee on Immunization Practices (ACIP)

Summary

These recommendations update information on the vaccine and antiviral agents available for controlling influenza during the 1995–96 influenza season (superseding MMWR *1994;43(No. RR-9)1–13 and* MMWR *1994;43(No. RR-15):1–10). The principal changes include information about a) the influenza virus strains included in the trivalent vaccine for 1995–96, b) side effects and adverse reactions, and c) the vaccination of pregnant women.*

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 (see Groups at Increased Risk for Influenza-Related Complications under Target Groups for Special Vaccination Programs) are more likely than the general population to require hospitalization. During major epidemics, hospitalization rates for persons at high risk may increase twofold to fivefold, depending on the age group. Previously healthy children and younger adults may also require hospitalization for influenza-related complications, but the relative increase in their hospitalization rates is less than for persons who belong to high-risk groups.

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. It is estimated that >20,000 influenza-associated deaths occurred during each of 10 different U.S. epidemics from 1972–73 to 1990–91, and >40,000 influenza-associated deaths occurred during each of three of these epidemics. More than 90% of the deaths attributed to pneumonia and influenza occurred among persons ≥65 years of age.

Because the proportion of elderly persons in the U.S. population is increasing and because age and its associated chronic diseases are risk factors for severe influenza illness, the number of deaths from influenza can be expected to increase unless control measures are implemented more vigorously. The number of persons <65 years of age at increased risk for influenza-related complications is also increasing. Better survival rates for organ-transplant recipients, the success of neonatal intensive-care units, and better management of diseases such as cystic fibrosis and acquired immunodeficiency syndrome (AIDS) result in a higher survival rate for younger persons at high risk.

OPTIONS FOR THE CONTROL OF INFLUENZA

In the United States, two measures are available that can reduce the impact of influenza: immunoprophylaxis with inactivated (killed-virus) vaccine and chemoprophylaxis or therapy with an influenza-specific antiviral drug (amantadine or rimantadine). Vaccination of persons at high risk each year before the influenza season is currently 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. When vaccine and epidemic strains of virus are well matched, achieving high vaccination rates among persons living in closed settings (e.g., nursing homes and other chronic-care facilities) can reduce the risk for outbreaks by inducing herd immunity.

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. To minimize febrile reactions, only subvirion or purified-surface–antigen preparations should be used for children; any of the preparations may be used for adults.

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 there is a good match between vaccine and circulating viruses, influenza vaccine has been shown to prevent illness in approximately 70% of healthy persons <65 years of age. In these circumstances, studies have also 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%–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.

RECOMMENDATIONS FOR THE USE OF INFLUENZA VACCINE

Influenza vaccine is strongly recommended for any person ≥6 months of age 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 should also be vaccinated. In addition, influenza vaccine may be administered to any person who wishes to reduce the chance of becoming infected with influenza. The trivalent influenza vaccine prepared for the 1995–96 season will include A/Texas/36/91-like (H1N1), A/Johannesburg/33/94-like (H3N2), and B/Beijing/184/93-like hemagglutinin antigens. The actual influenza type B strain used by U.S. manufacturers is B/Harbin/07/94, which is antigenically equivalent to the B/Beijing/184/93 strain. Guidelines for the use of vaccine among certain patient populations follow. Dosage recommendations are also summarized (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 in the year following vaccination. Because the 1995–96 vaccine differs from the 1994–95 vaccine, supplies of 1994–95 vaccine should not be administered to provide protection for the 1995–96 influenza season.

Two doses administered at least 1 month apart may be required for satisfactory antibody responses among previously unvaccinated children <9 years of age; 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 the past decade, 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

To maximize protection of high-risk persons, they and their close contacts should be targeted for organized vaccination programs.

Groups at Increased Risk for Influenza-Related Complications:

- Persons ≥65 years of age
- Residents of nursing homes and other chronic-care facilities that house persons of any age with chronic medical conditions
- Adults and children with 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 (6 months–18 years of age) who are receiving long-term aspirin therapy and therefore might be at risk for developing Reye syndrome after influenza

TABLE 1. Influenza vaccine* dosage, by age group — United States, 1995–96 season

Age group	Product†	Dosage	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/Texas/36/91-like (H1N1), A/Johannesburg/33/94-like (H3N2), and B/Beijing/184/93-like hemagglutinin antigens in each 0.5 mL. The actual influenza type B strain used by U.S. manufacturers is B/Harbin/07/94, which is antigenically equivalent to the B/Beijing/184/93 strain. Manufacturers include: Connaught Laboratories, Inc. (Fluzone® whole or split); Evans Medical Ltd. (distributed by Adams Laboratories, Inc.) (Fluviron™ purified surface antigen vaccine); Parke-Davis (Fluogen® split); and Wyeth-Ayerst Laboratories (Flushield™ split). For further product information call Connaught, (800) 822-2463; Adams, (800) 932-1950; Parke-Davis, (800) 223-0432; Wyeth-Ayerst, (800) FLU-SHIELD.

†Because of the lower 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.

§The recommended site of vaccination is the deltoid muscle for adults and older children. 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.

Groups that Can Transmit Influenza to Persons at High Risk

Persons who are clinically or subclinically infected and who care for or live with members of high-risk groups can transmit influenza virus to them. 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

General Population

Physicians should administer influenza vaccine to any person who wishes to reduce the likelihood of becoming ill with influenza. 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.

Pregnant Women

Influenza-associated excess mortality among pregnant women has not been documented except during the pandemics of 1918–19 and 1957–58. However, additional case reports and limited studies suggest that women in the third trimester of pregnancy and early puerperium, including those women without underlying risk factors, might be at increased risk for serious complications from influenza. Health-care workers who provide care for pregnant women should consider administering influenza vaccine to all women who would be in the third trimester of pregnancy or early puerperium during the influenza season. 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. Administration of influenza vaccine is considered safe at any stage of pregnancy.

Persons Infected with Human Immunodeficiency Virus (HIV)

Limited information exists regarding the frequency and severity of influenza illness among HIV-infected persons, but reports suggest that symptoms might be prolonged and the risk for complications increased for some HIV-infected persons. Because influenza can result in serious illness and complications, vaccination is a prudent

precaution and will result in protective antibody levels in many recipients. However, the antibody response to vaccine can be low in persons with advanced HIV-related illnesses; a booster dose of vaccine does not improve the immune response for these persons.

Foreign Travelers

The risk for exposure to influenza during foreign travel 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, 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 the high-risk categories should be especially 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.

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 (i.e., 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 reported by fewer than one third of vaccinees is soreness at the vaccination site that lasts for up to 2 days. In addition, two types of systemic reactions have occurred:

- Fever, malaise, myalgia, and other systemic symptoms occur infrequently 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;

- Immediate—presumably allergic—reactions (e.g., hives, angioedema, allergic asthma, and systemic anaphylaxis) occur rarely after influenza vaccination. These reactions probably result from hypersensitivity to some vaccine component; the majority of reactions are most likely related to 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 with 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 developed by Murphy and Strunk may be considered for patients who have egg allergies and medical conditions that place them at increased risk for influenza-associated complications (Murphy and Strunk, 1985).

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 has usually consisted of local, delayed-type hypersensitivity reactions.

Unlike the 1976 swine influenza vaccine, subsequent vaccines prepared from other virus strains have not been clearly associated with an increased frequency of Guillain-Barré syndrome (GBS). However, a precise estimate of risk is difficult to determine for a rare condition such as GBS, which has an annual background incidence of only one to two cases per 100,000 adult population. Among persons who received the swine influenza vaccine, the rate of GBS that exceeded the background rate was slightly less than one case per 100,000 vaccinations.

An investigation of GBS cases in 1990–91 indicated no overall increase in frequency of GBS among persons who were administered influenza vaccine; a slight increase in GBS cases among vaccinated persons might have occurred in the age group 18–64 years, but not among persons ≥65 years of age. In contrast to the swine influenza vaccine, the epidemiologic features of the possible association of the 1990–91 vaccine with GBS were not as convincing. The rate of GBS cases after vaccination that was passively reported to the Vaccine Adverse Event Reporting System (VAERS) during 1993–94 was estimated to be approximately twice the average rate reported during other recent seasons (i.e., 1990–91, 1991–92, 1992–93 and 1994–95). The data currently available are not sufficient to determine whether this represents an actual risk. However, even if GBS were a true side effect, the very low estimated risk for GBS is less than that for severe influenza that could be prevented by vaccination.

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. Although it would seem prudent to avoid a subsequent influenza vaccination in a person known to have developed GBS within 6 weeks of a previous influenza vaccination, for most persons with a history of GBS who are at high risk for severe complications from influenza, the established benefits of influenza vaccination justify yearly immunization.

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 both 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 (DTP or DTaP). Because influenza vaccine can cause fever when administered to young children, DTaP might be preferable in those children ≥15 months of age who are receiving the fourth or fifth dose of pertussis vaccine. DTaP is not licensed for the initial three-dose series of pertussis vaccine.

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 mid-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 <9 years of age 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

Although rates of influenza vaccination have increased in recent years, surveys indicate that less than half of the high-risk population receives influenza vaccine each year. More effective strategies are needed for delivering vaccine to persons at high risk and to their health-care providers and household contacts.

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. Persons for whom influenza vaccine is recommended can be identified and vaccinated in the settings described in the following paragraphs.

Outpatient Clinics and Physicians' Offices

Staff in physicians' offices, clinics, health-maintenance organizations, and employee health clinics should be instructed to 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 vaccine. If possible, arrangements should be made to provide vaccine with minimal waiting time and at the lowest possible cost.

Facilities Providing Episodic or Acute Care

Health-care providers in these settings (e.g., emergency rooms and walk-in clinics) should be familiar with influenza vaccine recommendations. They should offer vaccine to persons in high-risk groups or should provide written information on why, where, and how to obtain the vaccine. Written information should be available in language(s) appropriate for the population 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 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 ≥65 years of age 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.

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 provided in the home if necessary. Caregivers and other persons in the household (including children) should be referred for vaccination.

Facilities Providing Services to Persons ≥65 Years of Age

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

Clinics and Others Providing Health Care for Travelers

Indications for influenza vaccination should be reviewed before travel, and vaccine should be offered if appropriate (see Foreign Travelers).

Health-Care Workers

Administrators of all health-care facilities should arrange for influenza vaccine to be offered to all personnel before the influenza season. Personnel should be provided with appropriate educational materials and strongly encouraged to receive vaccine. Particular emphasis should be placed on vaccination of persons who care for members of high-risk groups (e.g., staff of intensive-care units [including newborn intensive-care units], staff of medical/surgical units, and employees of nursing homes and chronic-care facilities). Using a mobile cart to take vaccine to hospital wards or other work sites and making vaccine available during night and weekend work shifts can enhance compliance, as can a follow-up campaign early in the course of a community outbreak.

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 prior to approval, amantadine is indicated for treatment and prophylaxis of adults and children ≥1 year of age. Rimantadine was approved in 1993 for treatment and prophylaxis in adults but was approved only for prophylaxis in 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 are rarely 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 (see Considerations for Selecting Amantadine or Rimantadine for Chemoprophylaxis or Treatment).

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 can still 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 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 influenza 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

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. Insufficient data exist to determine the efficacy of rimantadine treatment in children. Thus, rimantadine is currently approved only for prophylaxis in 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 saved 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 preapproved 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 dose for each resident should be determined after consulting the dosage recommendations and precautions (see Considerations for Selecting Amantadine or Rimantadine for Chemoprophylaxis or Treatment) 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 due to 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/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 kidney.

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 lightheadedness) 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 dose of 200 mg/day experienced at least one CNS symptom, compared with approximately 14% of those taking the same dose of amantadine and 4% of those taking placebo. The incidence of gastrointestinal side effects (e.g., nausea and anorexia) is approximately 3% among persons taking either drug, compared with 1%–2% among 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 dose 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 only recently been approved for marketing, 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. The following are guidelines for the use of amantadine and rimantadine in certain patient populations. Dosage recommendations are also summarized (Table 2).

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. 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 little to drug clearance.

TABLE 2. Recommended dosage for amantadine and rimantadine treatment and prophylaxis

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

NOTE: Amantadine manufacturers include: Dupont Pharma (Symmetrel®—syrup); Solvay Pharmaceuticals (Symadine™—capsule); Chase Pharmaceuticals and Invamed (Amantadine HCL—capsule); and Copley Pharmaceuticals, Barre National, and Mikart (Amantadine HCL—syrup). Rimantadine is manufactured by Forest Laboratories (Flumandine®—tablet and syrup).

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

† 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 dose of 5 mg/kg/day.

¶ A reduction in dose 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 dose 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.

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 controls of the same age. Hemodialysis did not contribute to drug clearance. In studies among 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 ≥65 Years of Age

Amantadine

Because renal function declines with increasing age, the daily dose for persons ≥65 years of age 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 dose of 200 mg/day compared with elderly persons taking the same dose 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 two to four times greater than those reported in younger adults.

The dosage of rimantadine should be reduced to 100 mg/day for treatment or prophylaxis of elderly nursing-home residents. Although further studies are needed to determine the optimal dose for other elderly persons, a reduction in dosage to 100 mg/day should be considered for all persons ≥65 years of age 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 with liver disease.

Rimantadine

The safety and pharmacokinetics of rimantadine have only been evaluated 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, in persons with severe liver dysfunction, the apparent clearance of rimantadine was 50% lower than that reported for persons without liver disease. A dose 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

In clinical trials, seizures (or seizure-like activity) have been observed in a few 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, because such persons have usually been excluded from participating in clinical trials of rimantadine.

Children

Amantadine

The use of amantadine in children <1 year of age has not been adequately evaluated. The FDA-approved dosage for children 1–9 years of age 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 ≥10 years of age 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 in children <1 year of age has not been adequately evaluated. In children 1–9 years of age, 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 ≥10 years of age 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.

Drug Interactions

Amantadine

Careful observation is advised when amantadine is administered concurrently with drugs that affect the CNS, especially CNS stimulants.

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), telephone (404) 332-4551, or through the CDC Information Service on the Public Health Network electronic bulletin board. 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.

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