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# Recommendations of the Immunization Practices Advisory Committee Prevention and Control of Influenza

These recommendations update information on the vaccine and antiviral agent available for controlling influenza during the 1988-89 influenza season (superseding MMWR 1987;36:373-80,385-7). Changes include statements about 1) updating of the influenza strains in the trivalent vaccine for 1988-89, 2) increased emphasis on the need for vaccination of health-care workers, 3) prevention of influenza in persons with human immunodeficiency virus (HIV) infection, and 4) dosage considerations for amantadine.

## INTRODUCTION

Influenza A viruses are classified into subtypes on the basis of two antigens: hemagglutinin (H) and neuraminidase (N). Three subtypes of hemagglutinin (H1, H2, H3) and two subtypes of neuraminidase (N1, N2) are recognized among influenza A viruses that have caused widespread human disease. Immunity to these antigens, especially the hemagglutinin, reduces the likelihood of infection and the severity of disease if infection occurs. However, over time there may be enough antigenic variation (antigenic drift) within the same subtype 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 current strains provide the basis for selecting virus strains included in each year's vaccine.

Typical influenza illness is characterized by abrupt onset of fever, sore throat, and nonproductive cough. Unlike many other common respiratory infections, it can cause extreme malaise lasting several days. More severe illness can result if influenza virus invades the lungs (primary viral pneumonia) or if secondary bacterial pneumonia occurs. High attack rates of acute illness and lower-respiratory-tract complications during influenza epidemics usually result in dramatic increases in visits to physicians' offices, walk-in clinics, and emergency rooms by persons of all ages.

Elderly persons and those with underlying health problems are at increased risk for complications of influenza infection. Such high-risk persons are more likely than the general population to require hospitalization if infected. One recent study showed that, during major epidemics, hospitalization rates for high-risk adults increased twofold to fivefold, depending on age group. Previously healthy children and younger adults occasionally are hospitalized for influenza-related complications, but the relative increase in their hospitalization rates is much

less than that for high-risk groups.

A significant increase in mortality further indicates the impact of influenza epidemics. This increase is a direct result not only of pneumonia, but also of cardiopulmonary or other chronic diseases that can be exacerbated by influenza infection. Ten thousand or more excess deaths have been documented in each of 19 different epidemics during the years 1957-1986; more than 40,000 excess deaths occurred in each of several recent epidemics. Approximately 80%-90% of the excess deaths attributed to pneumonia and influenza were among persons greater than or equal to 65 years of age; however, influenza-associated deaths have also been reported among children or previously healthy adults less than 65 years of age during major epidemics.

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 toll from influenza can be expected to increase unless control measures are used more vigorously. The number of younger persons at high risk for infection-related complications is also increasing for various reasons, such as the success of neonatal intensive-care units, better management of diseases such as cystic fibrosis, better survival rates for organ-transplant recipients, and the spread of HIV infection.

## OPTIONS FOR THE CONTROL OF INFLUENZA

Two measures are available in the United States to reduce the impact of influenza: immunoprophylaxis with inactivated (killed-virus) vaccine and chemoprophylaxis or therapy with the antiviral drug amantadine. Vaccination of high-risk persons each year before the influenza season is the single most important measure for reducing the impact of influenza. Vaccination can be highly cost-effective 1) when it is aimed at individuals who experience the most severe consequences and who have a higher- than-average risk of infection and 2) when it is administered to high-risk individuals during routine health-care visits before the influenza season, making special visits to physicians' offices or clinics unnecessary. Recent reports indicate that, when there is a good match between vaccine and epidemic strains of virus, achieving high vaccination rates in closed populations can reduce the risk of outbreaks by inducing herd immunity. When outbreaks of influenza A do occur in closed populations, they can be stopped by chemoprophylaxis for all residents.

Other indications for prophylaxis (whether with vaccine or amantadine) include the strong desire of any person to avoid an influenza infection, reduce the severity of disease, or reduce the chances of transmitting influenza to high-risk persons with whom they have frequent contact. Unlike vaccine, which protects against influenza types A and B, amantadine is effective only against influenza A.

Amantadine therapy is most likely to benefit persons who seek medical attention shortly after the abrupt onset of an acute respiratory infection during an influenza A epidemic. Early amantadine therapy may reduce the severity and duration of illness in high-risk individuals who have not been vaccinated or who were not protected by vaccination.

Influenza is known to be transmitted in medical settings. Measures such as using isolation precautions for ill patients individually or in groups, limiting visitors, and avoiding elective admissions and surgery during an influenza outbreak may limit further transmission of virus within hospitals and other institutions. However, unlike amantadine prophylaxis, these measures have not been shown to be effective in controlling outbreaks. Likewise, the effectiveness of closing schools or classrooms during explosive outbreaks has not been established.

## INACTIVATED VACCINE FOR INFLUENZA A AND B

Influenza vaccine is made from highly purified, egg-grown viruses that have been rendered noninfectious (inactivated). Most vaccines distributed in the United States have been chemically treated (split-virus preparations) to reduce the incidence of febrile reactions in children. Influenza vaccine currently contains three virus strains (two type A and one type B) representing influenza viruses recently circulating worldwide and believed likely to circulate in the United States the following winter. The potency of the present vaccine is such that it causes minimal systemic or febrile reactions. Most vaccinated young adults develop hemagglutination-inhibition antibody titers that are likely to protect them against infection by strains like those in the vaccine and,

often, by related variants that may emerge. Elderly persons and persons with certain chronic diseases may develop lower postvaccination antibody titers than healthy young adults and, thus, may be more susceptible to upper-respiratory-tract infection. Nevertheless, influenza vaccine can still be effective in preventing lower-respiratory-tract involvement or other complications, thereby reducing the risk of hospitalization and death.

## RECOMMENDATIONS FOR USE OF INACTIVATED INFLUENZA VACCINE

Influenza vaccine is recommended for 1) high-risk persons greater than or equal to 6 months of age and their medical-care providers or household contacts; 2) children and teenagers receiving long-term aspirin therapy who, therefore, may be at increased risk of developing Reye syndrome after an influenza virus infection; and 3) other persons who wish to reduce their chances of acquiring influenza. Vaccine composition and dosages for the 1988-89 season are given in Table 1. Guidelines for the use of vaccine among different groups are given below.

Remaining 1987-88 vaccine should not be used. Although the current influenza vaccine often contains one or more antigens used in previous years, immunity declines in the year following vaccination. Therefore, annual vaccination is required.

During the past decade, data on influenza vaccine immunogenicity and side effects have generally been obtained when vaccine has been administered intramuscularly. Because there has been no adequate evaluation of recent influenza vaccines administered by other routes, the intramuscular route should be used. Adults and older children should be vaccinated in the deltoid muscle, and infants and young children, in the anterolateral aspect of the thigh.

**TARGET GROUPS FOR SPECIAL VACCINATION PROGRAMS** Groups at greatest risk of influenza-related complications:

1. Adults and children with chronic disorders of the pulmonary or cardiovascular systems requiring regular medical follow-up or hospitalization during the preceding year, including children with asthma.
2. Residents of nursing homes and other chronic-care facilities housing patients of any age with chronic medical conditions. Groups at moderate risk of influenza-related complications:
3. Otherwise healthy persons greater than or equal to 65 years old.
4. 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.
5. Children and teenagers (aged 6 months-18 years) who are receiving long-term aspirin therapy and, therefore, may be at risk of contracting Reye syndrome after an influenza infection. Groups potentially capable of nosocomial transmission of influenza to high-risk persons. Individuals attending high-risk persons can transmit influenza infections to them while they are themselves incubating infection, undergoing subclinical infection, or working despite the existence of symptoms. Some high-risk persons (e.g., the elderly, transplant recipients, or persons with acquired immunodeficiency syndrome (AIDS)) can have relatively low antibody responses to influenza vaccine. Efforts to protect them against influenza may be improved by reducing the chances that their care providers may expose them to influenza. Therefore, the following groups should be vaccinated:
6. Physicians, nurses, and other personnel who have extensive contact with high-risk patients (e.g., primary-care and certain specialty clinicians and staff of chronic-care facilities and intensive-care units, particularly neonatal intensive-care units).
7. Providers of home care to high-risk persons (e.g., visiting nurses, volunteer workers) as well as all household members of high-risk persons, including children, whether or not they provide care.

## VACCINATION OF OTHER GROUPS

**General Population:** Physicians should administer influenza vaccine to any person who wishes to reduce his/her chances of acquiring influenza infection. Persons who provide essential community services may be considered for vaccination to minimize the disruption of essential activities during severe epidemics.

**Pregnant Women:** Pregnancy has not been shown to be a risk factor for severe influenza infection, except in the largest pandemics of 1918-19 and 1957-58. However, pregnant women who have medical conditions that increase their risks of complications from influenza should be vaccinated, as the vaccine is considered safe for pregnant women. Administering the vaccine after the first trimester is a reasonable precaution to minimize any concern over the theoretical possibility of teratogenicity. However, it is undesirable to delay vaccination of pregnant women with high-risk conditions who will still be in the first trimester of pregnancy when the influenza season begins.

**Persons infected with human immunodeficiency virus (HIV):** Increases in infections and complications caused by various respiratory pathogens have been observed in persons infected with HIV. However, similar increases due to influenza have not been reported during recent epidemics. Nevertheless, because influenza may result in serious illness and complications in some HIV-infected persons, vaccination is a prudent precaution.

## PERSONS WHO SHOULD NOT BE VACCINATED

Inactivated influenza vaccine should not be given to persons who have an anaphylactic hypersensitivity to eggs (see Side Effects and Adverse Reactions below). Persons with acute febrile illnesses normally should not be vaccinated until their temporary symptoms have abated.

## TIMING OF INFLUENZA VACCINATION ACTIVITIES

Influenza vaccine should be offered beginning in September. Except in years of pandemic influenza (e.g., 1957 and 1968), high levels of influenza activity generally do not occur in the contiguous 48 states before December. Therefore, organized vaccination campaigns where high-risk persons are routinely accessible are optimally undertaken in November. In facilities such as nursing homes, it is particularly important to avoid administering vaccine too far in advance of the influenza season because antibody can begin to decline within a few months. Such vaccination programs may be undertaken in September or October if regional influenza activity is expected to begin earlier than normal.

Children less than or equal to 12 years of age who have not been vaccinated previously require two doses with at least 1 month between doses. The second dose should be given before December. Vaccine can be given to both children and adults up to and even after influenza virus activity is documented in a region.

## STRATEGIES FOR IMPLEMENTING INFLUENZA VACCINE RECOMMENDATIONS

More effective programs are needed for giving influenza vaccine to high-risk persons, their health-care providers, and their household contacts. Programs for administering vaccine in nursing homes and other chronic-care facilities, physicians' offices, health maintenance organizations, hospitals, and employee health clinics must be carefully planned. High-risk adults and children who do not live in nursing homes or other chronic-care facilities should be offered influenza vaccine at their last regular medical appointment before the influenza season (i.e., before December). If they do not have a regular medical appointment scheduled in the fall, they should be notified by their health-care providers to come in specifically to receive influenza vaccine. From September through February, hospital discharge procedures should include influenza vaccination of high-risk patients. Medical-care personnel and support staff should ensure that no high-risk patient resides in or leaves a medical-care facility in the fall without being offered and urged to receive influenza vaccine. Equally important, administrators and infection-control staff of health-care facilities should establish procedures for offering vaccine to patient-care staff that take into account barriers to vaccination. More staff members will be vaccinated if vaccine is readily available at the worksite (e.g., on patient-care units during all shifts rather than at an employee health clinic).

Educational materials about influenza and its control are available from a variety of sources. For information on sources of educational materials and a selected bibliography, contact the Centers for Disease Control, Center for Prevention Services, Technical Information Services, 1600 Clifton Road, N.E., Atlanta, Georgia 30333.

## SIDE EFFECTS AND ADVERSE REACTIONS

Because influenza vaccine contains only noninfectious viruses, it cannot cause influenza. Occasional cases of respiratory disease following vaccination represent coincidental illnesses unrelated to influenza vaccination. The most frequent side effect of vaccination is soreness around the vaccination site for up to 1 or 2 days; this occurs in less than one-third of vaccinees.

In addition, the following two types of systemic reactions have occurred:

8. 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.
9. Immediate, presumably allergic, reactions such as hives, angioedema, allergic asthma, or systemic anaphylaxis occur extremely rarely after influenza vaccination. These reactions probably result from hypersensitivity to some vaccine component--most likely residual egg protein. Although current influenza vaccines contain only a small quantity of egg protein, they are presumed capable of inducing immediate hypersensitivity reactions in persons with severe egg allergy, and such persons should not be given influenza vaccine. This includes persons who develop hives, have swelling of the lips or tongue, or experience acute respiratory distress or collapse after eating eggs. Persons with a documented immunoglobulin E (IgE)-mediated hypersensitivity to eggs, including those who have experienced occupational asthma or other allergic responses from occupational exposure to egg protein, may also be at increased risk of reactions from influenza vaccine. Unlike the 1976 swine influenza vaccine, subsequent vaccines prepared from other virus strains have not been associated with an increased frequency of Guillain-Barre syndrome. Although influenza vaccination can inhibit the clearance of warfarin and theophylline, clinical studies have consistently failed to show any adverse effects attributable to these drugs in patients receiving influenza vaccine.

## SIMULTANEOUS ADMINISTRATION OF OTHER VACCINES, INCLUDING CHILDHOOD VACCINES

The target groups for influenza and pneumococcal vaccination overlap considerably. Both vaccines can be given at the same time at different sites without increasing side effects. However, influenza vaccine is given annually, and it is currently recommended that pneumococcal vaccine be given only once. Detailed immunization records should be provided to each patient to record the date when pneumococcal vaccine was given.

High-risk children usually see a health professional to receive routine pediatric vaccines. These visits provide a good opportunity to administer influenza vaccine simultaneously but in a different site. Although studies have not been conducted, simultaneous administration should not diminish immunogenicity or increase adverse reactions.

## ANTIVIRAL AGENTS FOR INFLUENZA A

Two antiviral drugs have specific activity against influenza A viruses: amantadine hydrochloride and rimantadine hydrochloride. Currently, only amantadine is approved for marketing in the United States.

Both amantadine and rimantadine interfere with the replication cycle of type A influenza viruses, although the specific mechanisms of their antiviral activity are not completely understood. Both drugs are 70%-90% effective in preventing illnesses caused by naturally occurring strains of type A influenza viruses.

However, they are not effective against type B influenza. When administered within 24-48 hours after the onset of illness, they can reduce the duration of fever and other systemic symptoms, allowing the patient to return more rapidly to routine daily activities. Since these drugs may not prevent infection itself, persons who take them can still develop immune responses that will protect them when they are subsequently exposed to antigenically related viruses.

Increasing the availability of rapid viral diagnostic tests and improving the dissemination of information about areas where influenza A virus infections have been confirmed will allow for more efficient and appropriate use of antiviral agents. Such information is reported throughout the influenza season in the MMWR and is also available by computer telecommunication through the Public Health Foundation.

## AMANTADINE PROPHYLAXIS RECOMMENDATIONS

Amantadine is recommended under certain circumstances, particularly for control of presumed influenza A outbreaks in institutions housing high-risk persons. Chemoprophylaxis should begin as early as possible after the outbreak is recognized. Contingency planning is needed in chronic-care facilities to establish specific steps for rapidly administering amantadine to residents and staff when influenza outbreaks occur. For outbreak control, amantadine should be administered to all residents of the institution whether or not they received influenza vaccine the previous fall. Amantadine should also be offered to unvaccinated staff who provide care to high-risk patients. For prophylaxis, the antiviral drug should be taken each day for the duration of influenza activity in the community.

Amantadine prophylaxis is also recommended in the following situations:

10. As an adjunct to late vaccination of high-risk persons. It is not too late to vaccinate even when influenza A is known to be in the community. However, because the development of an antibody response following vaccination takes about 2 weeks, amantadine should be used during this period. Amantadine does not interfere with the antibody response to the vaccine.
11. To reduce the spread of infection and to maintain care for high-risk persons in the home. Unvaccinated persons who provide home care for high-risk persons (e.g., household members, visiting nurses, volunteer workers) should also receive amantadine prophylaxis during the period when influenza A outbreaks occur.
12. For immunodeficient persons. As a supplement to the protection afforded by vaccination, amantadine prophylaxis is indicated for high-risk patients who may have a poor antibody response to influenza vaccine, such as persons with AIDS. Whereas adults with AIDS can be expected to have some residual immunity to influenza from prior infections, children with AIDS may have little or no immunity to the virus. Therefore, amantadine prophylaxis against influenza should be considered during influenza epidemics, especially for children with AIDS. The potential benefits should be evaluated on a case-by-case basis, taking into account the potential risks of side effects, especially in patients with central nervous system involvement.
13. For persons for whom influenza vaccine is contraindicated (see Side Effects and Adverse Reactions above). Amantadine can also be used prophylactically in other situations (e.g., for unimmunized members of the general population who wish to avoid influenza A illness). This decision should be made on an individual basis.

## AMANTADINE THERAPY

Although amantadine has been shown to reduce the severity and shorten the duration of influenza A illness in healthy adults and children, no well-controlled clinical studies have examined the efficacy of amantadine therapy in preventing complications of influenza A in high-risk persons. Nevertheless, because of the potential benefits, amantadine should be considered for high-risk patients who contract an illness compatible with influenza during a period of known or suspected influenza A activity in the community. The drug should be given within 24-48 hours after onset of illness and should be continued until 48 hours

after signs and symptoms resolve.

## DOSAGE CONSIDERATIONS FOR AMANTADINE

The following information should be considered in determining the appropriate dosage of amantadine:\*

14. In controlled studies, 5%-10% of healthy young adults taking amantadine at the standard adult dosage of 200 mg per day have reported side effects including nausea, dizziness, insomnia, nervousness, and impaired concentration. Data suggest that a daily prophylactic dosage of 100 mg may provide protection comparable to that of 200 mg/day but with fewer side effects. No studies have compared the efficacy of amantadine at daily dosages of 100 mg and 200 mg for treatment of influenza A infection.
15. Amantadine is not metabolized and is excreted unchanged in the urine by glomerular filtration and tubular secretion. Because renal function declines with aging, the daily dosage for persons greater than or equal to 65 years of age should not exceed 100 mg for prophylaxis or treatment. When amantadine is administered to patients with impaired renal function, the dosage should be further reduced (see package insert). Because recommended dosages for persons with renal impairment provide only a rough estimate of the optimal dosage for a given patient, such individuals should be closely observed so that adverse reactions can be recognized promptly and the dosage reduced or the drug discontinued if necessary.
16. Persons with active seizure disorders may be at increased risk for seizures when given amantadine at a dosage of 200 mg daily. Data suggest that the risk of seizures in such persons might be reduced by using a lower dose of the drug.
17. The use of amantadine in children less than 1 year of age has not been adequately evaluated. The approved dosage for children 1-9 years of age is 4.4 mg/kg/day, not to exceed 150 mg/day. Although further studies would be desirable to determine the optimal dosage for children, physicians should consider prescribing 4.4 mg/kg/day to reduce the risk of toxicity. For children greater than or equal to 10 years weighing less than 45 kg, it may also be advisable to prescribe 4.4 mg/kg/day. The dose for treatment should not exceed 150 mg for children aged 1-9 years and 200 mg for children greater than or equal to 10 years of age. As for adults, a maximum dosage of 100 mg daily should be effective for prophylaxis (see #1 above). \*Further information is available from DuPont Pharmaceuticals, one of the manufacturers of amantadine, by calling (800)441-9861.

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