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Prevention and Control of Influenza

Recommendation of the Immunization Practices Advisory Committee (ACIP) of the U.S. Public Health Service

These recommendations of the Immunization Practices Advisory Committee (ACIP) update for 1985-86 the information on the vaccine and antiviral agent available for control of influenza. Changes include addition of statements about: (1) the route of vaccine administration; (2) the use of amantadine in medical personnel during influenza A outbreaks; (3) the need to prepare contingency plans to expedite use of amantadine in aborting influenza A outbreaks among residents of institutions; and (4) reduction in the dosage of amantadine for older patients or persons with seizure disorders.

Introduction

Influenza viruses have continually demonstrated an ability to cause major epidemics of respiratory disease. Typical influenza illness is characterized by abrupt onset of fever, sore throat, and nonproductive cough, and unlike many other common respiratory infections, can cause extreme malaise lasting several days. More severe disease can result from invasion of the lungs by influenza virus (primary viral pneumonia) or by secondary bacterial pneumonia. High attack rates of acute illness and the frequent occurrence of lower respiratory tract complications usually result in dramatic rises in visits to physicians' offices and hospital emergency rooms. Furthermore, influenza frequently infects individuals who, because of their ages or underlying health problems, are poorly able to cope with the disease and often require medical attention, including hospitalization. Such persons are considered to be medically at "high risk" in epidemics. In one recent study, for example, hospitalization rates for adults with high-risk medical conditions increased during major epidemics by about twofold to fivefold in different age groups, reaching a maximum rate of about 800 excess hospitalizations per 100,000 high-risk persons.

A further indication of the impact of influenza epidemics is the significant increase that often occurs in mortality. Such excess mortality is attributed not only to the direct cause of influenza pneumonia but also to an increase in deaths from cardiopulmonary disease. Ten thousand or more excess deaths have been associated with epidemics 17 times from 1957 to 1984. Excess mortality again exceeded the epidemic threshold during the 1984-1985 influenza season. About 90% of the excess deaths attributed to pneumonia and influenza during epidemics occur among persons 65 years of age or older.

The greatest impact of influenza is normally seen when new strains appear against which most of the population lacks immunity. In these circumstances (e.g., 1957 and 1968), pandemics occur, and a quarter or more of the U.S. population was affected over 2-3 months.

Because of the increasing proportion of elderly persons in the U.S. population, and because age and its associated chronic diseases are risk factors for severe influenza illness, the future toll from influenza may increase, unless control measures are used more vigorously than in the past. Other populations at high risk for influenza-related complications are also increasing because of such factors as the success of intensive-care units for neonates, better management of diseases (such as cystic fibrosis), and better survival rates for organ transplant recipients. This statement discusses the presently available medical control measures, immunoprophylaxis with vaccines, and prophylaxis or therapy with the antiviral drug, amantadine.

Options For The Control of Influenza

For about 20 years, efforts to reduce the impact of influenza in the United States have been aimed primarily at immunoprophylaxis of persons at greatest risk of serious illness or death. Observations during influenza epidemics indicate that most influenza-related deaths occur among: (1)persons older than 65 years of age;

and (2) persons with chronic underlying disorders of the cardiovascular, pulmonary, and/or renal systems, as well as those with metabolic diseases (including diabetes mellitus), severe anemia, and/or compromised immune function. Recommendations listed below apply primarily to these high-risk groups. In addition, measures are described that apply to other individuals or groups under special circumstances. Influenza control options should also be made available to individuals who wish to reduce their chances of acquiring influenza infection or to reduce the severity of disease.

Prophylaxis is likely to be achieved with greatest cost-effectiveness by vaccinating individuals for whom infection may have the most severe consequences and for whom there is a higher than average potential for infection. In addition, vaccination can best be organized when such high-risk individuals routinely have contact with the health-care delivery system for reasons other than acute respiratory infection before the influenza season, thereby permitting vaccine administration without special visits to doctors' offices or clinics. Other indications for prophylaxis (whether with vaccine or antiviral drugs) include the strong desire of any person to avoid a preventable illness.

The presently available specific therapy for influenza A, amantadine hydrochloride (Symmetrel®), is most likely to benefit individuals who seek medical attention promptly because of abrupt onset of an acute respiratory infection with troublesome symptoms during an influenza A epidemic. For high-risk individuals for whom influenza vaccine has not been used or has not prevented infection, amantadine therapy should be effective in reducing the severity of disease.

Inactivated Influenza Vaccine

Use of inactivated influenza vaccine is the single most important measure in preventing and/or attenuating influenza infection. Potency of present vaccines is such that nearly all 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 emerge. The elderly, the

very young, and patients with certain chronic diseases may develop lower postvaccination antibody titers than young adults. Under these circumstances, however, influenza vaccine may be more effective in preventing lower respiratory tract involvement or other complications of influenza than in preventing infection and involvement of the upper respiratory tract. Influenza vaccine will not prevent primary illness caused by other respiratory pathogens.

Annual vaccination against influenza has been recommended since 1963 for individuals at high risk of lower respiratory tract complications and death following influenza infection, i.e., the elderly and persons with chronic disorders of the cardiovascular, pulmonary, and/or renal systems, metabolic diseases, severe anemia, and/or compromised immune function. These groups have been identified primarily by reviews of death certificate data, supported by hospital-based or population-based studies. Each group encompasses patients along a continuum of underlying general health. In other words, within each broadly defined high-risk category, some persons may be more likely than others to develop severe complications from influenza infection.

Investigations of influenza outbreaks in nursing homes, for example, have demonstrated attack rates as high as 60%, with case-fatality ratios of 30% or more. Chronic diseases and other debilitating conditions are common among nursing home residents, and spread of infection can often be explosive in such relatively crowded and closed environments. Recent retrospective studies of noninstitutionalized patients also suggest that chronic underlying diseases, particularly those that affect the cardiovascular and pulmonary systems, may contribute more to the severity of illness than age alone. Since influenza infections are also known to invoke abnormalities in gas exchange and peripheral airways dysfunction in adults, children with compromised pulmonary function, including those with cystic fibrosis, chronic asthma, and bronchopulmonary dysplasia, as well as neonates in intensive-care units, may also be at higher risk of severe illness, although firm evidence is lacking. Children with congenital heart disease may also be considered at high risk, since respiratory viruses in general often produce severe infections in this population.

TABLE 1. Influenza vaccine* dosage by age of patient—United States, 1985-1986 season

Age group	Product†	Dosage§	No. doses	Route¶
6-35 mos.	Split virus only	0.25 ml	2**	IM
3-12 yrs.	Split virus only	0.5 ml	2**	IM
> 12 years	Whole or split virus	0.5 ml	1	IM

*Contains 15 µg each of A/Chile/83(H1N1), A/Philippines/82(H3N2), and B/USSR/83 hemagglutinin antigens in each 0.5 ml. Manufacturers include Parke-Davis (Fluogen® split), Squibb-Connaught (Fluzone® whole or split), Wyeth Laboratories (Influenza Virus Vaccine, Trivalent split). Manufacturer's phone numbers to obtain further product information are: Parke-Davis—(800) 223-0432; Squibb-Connaught—(800) 822-2463; Wyeth—(800) 321-2304.

†Because of the lower potential for causing febrile reactions, only split (subvirion) vaccine should be used in children. Immunogenicity and reactogenicity of split and whole virus vaccines are similar in adults when used according to the recommended dosage.

§Pneumococcal vaccine and influenza vaccine can be given at the same time at different sites without an increase in side effects, but it should be emphasized that, whereas influenza vaccine is given annually, pneumococcal vaccine should be given only once to adults. Detailed immunization records should be provided to each patient to help ensure that additional doses of pneumococcal vaccine are not given.

¶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 musculature.

**Four weeks or more between doses, both doses recommended for maximum protection. However, if the individual received at least one dose of any influenza vaccine recommended from 1978-79 to 1984-85, one dose is sufficient.

Target Groups for Vaccination

1. Based on the above observations, the previous, broadly defined high-risk group has been further classified on the basis of priority, so special efforts can be directed at providing vaccine to those who may derive the greatest benefit. Groups for which active, targeted vaccination efforts are most necessary are:
   a. Adults and children with chronic disorders of the cardiovascular or pulmonary systems that are severe enough to have required regular medical follow-ups or hospitalization during the preceding year.
   b. Residents of nursing homes and other chronic-care facilities (e.g., institutions housing patients of any age with chronic medical conditions).
2. Although not proven, it is reasonable to believe that medical personnel can transmit influenza infections to their high-risk patients while they are themselves incubating infection, undergoing subclinical infection, or working despite the existence of mild symptoms. In many winters, nosocomial outbreaks of influenza are reported. The potential for introducing influenza to high-risk groups, such as patients with severely compromised cardiopulmonary or immune systems or infants in neonatal intensive-care units, should be reduced by vaccination programs targeted at medical personnel. Therefore, physicians, nurses, and other personnel who have extensive contact with high-risk patients (e.g., primary-care and certain clinicians and staff of intensive-care units) should receive influenza vaccination annually.
3. After considering the needs of the above two target groups, high priority should also be given to organizing special programs making vaccine readily available to persons at moderately increased risk of serious illness compared with the general population:
   a. Otherwise healthy individuals over 65 years of age.
   b. Adults and children with chronic metabolic diseases (including diabetes mellitus), renal dysfunction, anemia, immunosuppression, or asthma that are severe enough to require regular medical follow-ups or hospitalization during the preceding year.

Vaccine Recommendations

Influenza vaccine is recommended for high-risk persons 6 months or older, for their medical-care personnel, and for other persons wishing to reduce their chances of acquiring influenza illness. Vaccine composition and doses are given in Table 1. Guidelines for use of vaccine are given below for different segments of the population. Although the 1985-1986 vaccine has the same formulation as the 1984-1985 vaccine, immunity declines in the year following vaccination. **Therefore, a history of vaccination for the 1984-1985 season does not preclude the need to be revaccinated for the 1985-1986 influenza season to provide optimal protection.**

Data on influenza immunogenicity and reactogenicity have generally been obtained when vaccine is administered by the intramuscular (deltoid) route. Because adequate evaluation of other routes in high-risk persons is lacking, the preferred route of vaccination is the deltoid muscle whenever possible.

High-Priority Target Groups

Annual vaccination with inactivated influenza vaccine is considered the single most important measure in preventing or attenuating influenza infection and is strongly recommended for persons at high risk and for those providing their medical care. In most past years, only 20% of the groups defined as high-risk on the basis of medical condition or age received influenza vaccine in any given year. Increased efforts must be made to immunize persons in high-risk groups, particularly those in the highest-priority target groups (see target group 1 above).

As an initial step, the ACIP recommends that infection-control programs in institutions for the aged or chronically ill have as their goal the achievement of no less than 80% vaccination rates for the residents. Hospitals and physicians should have a similar objective for vaccinating patients with severe cardiopulmonary disorders and for vaccinating medical personnel who have the greatest potential to introduce influenza virus into high-risk hospital settings (see target group 2 above). Wherever possible, efforts should also be made to vaccinate persons at moderately increased risk (see target group 3 above). This latter objective often requires that active promotion of influenza vaccine be made by individual physicians who practice outside organizations that can set administrative guidelines and procedures for their professional staff. Establishing systems for influenza vaccination activities in physicians' offices and clinics is essential in providing vaccine.

General population. Physicians should administer vaccine to any persons in their practices who wish to reduce their chances of acquiring influenza infection. Persons who provide essential community services, such as fire and police department employees, and health-care personnel are not considered to be at increased occupational risk of serious influenza illness but may be considered for vaccination programs designed to minimize the possible disruption of essential activities that can occur during severe epidemics.

Pregnant women. Pregnancy has not been demonstrated to be a risk factor for severe influenza infection, except in the largest pandemics of 1918-1919 and 1957-1958. Influenza vaccine is considered generally safe for pregnant women. Nonetheless, when vaccine is given during pregnancy, waiting until after the first trimester is a reasonable precaution to minimize any concern over the theoretical possibility of teratogenicity.

Persons who should not be vaccinated. Inactivated influenza vaccine should not be given to persons who have an anaphylactic sensitivity 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.

Strategies for Implementing Influenza Vaccine Recommendations

Influenza vaccine should normally be obtained to use during the fall. More effective programs for giving influenza vaccine are needed in nursing homes and other chronic-care facilities, in physicians' offices, and in hospital settings. Adults and children in high-priority target groups who do not

reside in nursing homes or other chronic-care facilities should be given influenza vaccine at the time of regular medical follow-ups in the fall. Those not scheduled for regular medical appointments in the fall should be notified by their medical offices or clinics to come in specifically to receive influenza vaccine. During the fall, physicians responsible for care of hospitalized patients should consider administering influenza vaccine to patients with high-risk conditions before the patients are discharged.

These and other programs to annually vaccinate target groups require planning well in advance and should, whenever possible, be completed before the beginning of the influenza season. However, vaccine can be given right up to the time influenza virus activity is documented, and even thereafter, although temporary chemoprophylaxis may be indicated in these situations (see **ANTIVIRAL AGENT: AMANTADINE** below).

Vaccine Composition

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 wide-spread human disease. Immunity to these antigens, especially hemagglutinin, reduces the likelihood of infection and the severity of disease if infection does occur. However, there may be sufficient antigenic variation (antigenic drift) within the same subtype over time, so 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 much more antigenic stability than influenza A viruses, antigenic variation does occur. As a consequence, the antigenic characteristics of current strains provide the basis for selecting virus strains included in the vaccine.

Based on the most recent epidemiologic and laboratory data (reported periodically in *MMWR* during the 1984-1985 influenza season), it is anticipated that strains prevalent in 1985-1986 will be closely related to A/Philippines/2/82(H3N2), A/Chile/1/83(H1N1), and B/USSR/100/83. Therefore, these strains will be included in the vaccine for use during the 1985-1986 season (Table 1). Although the components and their concentration in the 1985-1986 vaccine will be identical to those in the 1984-1985 vaccine, all 1984-1985 influenza vaccines released for civilian use have a June 30, 1985, expiration date. Remaining 1984-1985 vaccines should not be used beyond their expiration dates.

Side Effects and Adverse Reactions

Vaccines used in recent years have generally been associated with only a few reactions; fewer than one-third of vaccinees have been reported to develop local redness or induration for 1 or 2 days at the site of injection. Systemic reactions have been of two types:

1. Fever, malaise, myalgia, and other systemic symptoms of toxicity, although infrequent, most often affect children and others who have had no exposure to the influenza virus antigens contained in the vaccine. These reactions, which begin 6-12 hours after vaccination and persist for 1-2 days, are usually attributed to the influenza antigens (even though the virus is inactivated) and constitute most of the systemic side effects of influenza vaccination.
2. Immediate, presumably allergic, responses, such as flare and wheal or various respiratory tract symptoms of hypersensitivity, occur extremely rarely after influenza vaccination. These symptoms probably result from sensitivity to some vaccine component, most likely residual egg protein. Although current influenza vaccines contain only a small quantity of egg protein, on rare occasions, vaccine can induce hypersensitivity reactions. Individuals with anaphylactic hypersensitivity to eggs should *not* be given influenza vaccine. Such persons include those who, on eating eggs, develop swelling of the lips or tongue or experience acute respiratory dis-

tress or collapse. Unlike the 1976 swine influenza vaccine, subsequent vaccines have not been associated with an increased frequency of Guillain-Barré syndrome.

It has been reported that influenza vaccination may affect the clearances of warfarin and theophylline. Several studies, however, have failed to show any consistent adverse effect of influenza vaccination on patients taking these drugs.

Simultaneous Pneumococcal Vaccination

There is considerable overlap in the target groups for influenza vaccination and pneumococcal vaccine. Pneumococcal vaccine and influenza vaccine can be given at the same time at different sites without increased side effects, but it should be emphasized that, whereas influenza vaccine is given annually, pneumococcal vaccine should be given only once to adults. Detailed immunization records, which should be provided to each patient, will help ensure that additional doses of pneumococcal vaccine are not given.

Antiviral Agent: Amantadine

The only drug currently available for the specific prophylaxis and therapy of influenza virus infections is amantadine hydrochloride (Symmetrel®), which appears to interfere with the uncoating step in the virus replication cycle. The drug also reduces virus shedding. Amantadine is 70%-90% effective in preventing illnesses caused by circulating strains of type A influenza viruses (it is not effective against type B influenza). When administered within 24-48 hours after onset of illness, amantadine has been shown to reduce the duration of fever and other systemic symptoms with a more rapid return to routine daily activities and improvement in peripheral airway function. Since it may not prevent actual infection, persons who take the drug may still develop immune responses that will protect them when exposed to antigenically related viruses.

While considerable evidence shows that amantadine chemoprophylaxis is effective against influenza A, in most circumstances, it should not be used in lieu of vaccination, because it confers no protection against influenza B, and patient compliance could be a problem for continuous administration throughout epidemic periods, which generally last 6-12 weeks.

Amantadine prophylaxis recommendations. Specific circumstances for which amantadine prophylaxis is recommended include the following:

1. As short-term prophylaxis during the course of a presumed influenza A outbreak (e.g., in institutions for persons at high risk), particularly when the vaccine may be relatively ineffective (e.g., due to major antigenic changes in the virus). The drug should be given early in the outbreak in an effort to reduce the spread of the infection. Contingency planning for influenza outbreaks in institutions is needed to establish specific steps for rapid administration of amantadine when appropriate, including obtaining physicians' orders at short notice. When the decision to give amantadine for outbreak control is made, it is desirable to administer the drug to all residents of the affected institution, taking into account dosage recommendations and precautions given below and in the drug's package insert.
2. As an adjunct to late immunization of high-risk individuals. It is not too late to immunize even when influenza A is known to be in the community. However, since the development of a protective response following vaccination takes about 2 weeks, amantadine should be used in the interim. The drug is not known to interfere with antibody response to the vaccine.
3. To reduce disruption of medical care and to reduce spread of virus to high-risk persons when influenza A virus outbreaks occur. Amantadine prophylaxis is desirable for those physicians, nurses, and other personnel who have extensive contact with high-risk patients but who failed to receive the recommended annual influenza vaccination before the onset of influenza A activity. Such unprotected health-care workers should be immediately offered vaccine and provided amantadine for the subsequent 2 weeks while a protective response to vaccination develops. If vaccine is not given, is

TABLE 2. Amantadine hydrochloride (Symmetrel®) dosage, by age of patient and level of renal function

Age group	Dosage*
No recognized renal disease	
1-9 yrs.†	4.4-8.8 mg/kg/day once daily or divided twice daily. Total dosage should not exceed 150 mg/day.
10-64 yrs.§	200 mg once daily or divided twice daily
≥ 65 yrs.	100 mg once daily¶
Recognized renal disease	
Creatinine clearance: (ml/min 1.73m²)	
≥ 80	100 mg twice daily
60-79	200 mg/100 mg on alternate days
40-59	100 mg once daily
30-39	200 mg twice weekly
20-29	100 mg thrice weekly
10-19	200 mg/100 mg alternating every 7 days

*For prophylaxis, amantadine must be taken each day for the duration of influenza A activity in the community (generally 6-12 weeks). For therapy, amantadine should be started as soon as possible after onset of symptoms and should be continued for 24-48 hours after the disappearance of symptoms (generally 5-7 days).

†Use in children under 1 year has not been evaluated adequately. In one study, a dose of 6.6 mg/kg/day was reportedly well-tolerated by children over 2 years of age.

§Reduction of dosage to 100 mg/day is also recommended for persons with an active seizure disorder, because such persons may be at risk of experiencing an increase in the frequency of their seizures when given amantadine at 200 mg/day.

¶The reduced dosage of 100 mg/day for person 65 years of age or older without recognized renal disease is recommended to minimize the risk of toxicity, because renal function normally declines with age and because side effects have been reported more frequently in the elderly.

unavailable, or is of low efficacy due to a major antigenic change in the virus, amantadine prophylaxis should be continued throughout the period of influenza A activity in the community. Other health-care workers in hospitals should also be offered amantadine as long as this does not jeopardize the availability of the drug for prophylaxis of staff having greatest contact with high-risk patients.

4. To supplement protection afforded by vaccination in those with impaired immune responses. Chemoprophylaxis may be considered for high-risk patients who may be expected to have a poor antibody response to influenza vaccine, e.g., those with severe immunodeficiency.
5. As chemoprophylaxis throughout the influenza season for those few high-risk individuals for whom influenza vaccine is contraindicated because of anaphylactic hypersensitivity to egg protein or prior severe reactions associated with influenza vaccination.

Amantadine can also be used prophylactically in other situations (e.g., unimmunized members of the general population who wish to avoid influenza A illness). This decision should be made on an individual basis.

Therapy. Since vaccine efficacy is less than 100%, amantadine should be considered for therapeutic use, particularly for persons in the high-risk groups if they develop 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 of onset of illness and should be continued until 48 hours after resolution of signs and symptoms.

Persons who should not be given amantadine. Particular caution should be exercised for persons under 1 year of age, persons of any age with impaired renal function, or persons with an active seizure disorder (see below).

Dosage. The usual adult dosage of amantadine is 200 mg per day. Splitting the dose into 100 mg twice daily may reduce the frequency of side effects. Because renal function normally declines with age, and because side effects have been reported more frequently in older persons, a reduced dosage of 100 mg/day is generally advisable for persons aged 65 years and older to minimize the risk of toxicity. Dosages for children and for persons of any age with recognized renal disease are given in Table 2. Persons 10-

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64 years old without recognized renal disease but with an active seizure disorder may also be at risk of increased frequency of their seizures when given amantadine at 200 mg/day rather than 100 mg/day.

Side effects and adverse reactions. Five percent to 10% of otherwise healthy adults taking amantadine have reported side effects, such as insomnia, lightheadedness, irritability, and difficulty concentrating. These and other side effects (see package insert) may be more pronounced in patients with underlying diseases, particularly those common among the elderly; *provisions for careful monitoring are needed for these individuals* so that adverse effects may be recognized promptly and the drug reduced in dosage or discontinued, if necessary. Since amantadine is not metabolized, toxic levels will occur when renal function is sufficiently impaired.

Other Measures

Under special circumstances, supplementary control measures may be useful in further limiting the spread of influenza. Influenza is known to cause nosocomial infection; a number of measures, including isolation, cohorting of patients and personnel, limiting visitors, and avoiding elective admissions and surgery during an influenza outbreak, have all been suggested to limit further transmission. However, the effectiveness of most of these measures has not been conclusively demonstrated. Schools or classrooms have been closed occasionally when explosive outbreaks have occurred. The effect of this measure on virus transmission has not been established.

Tabulation of Reported Diseases to Follow

Readers will notice that this issue does not have the usual listing of reported diseases on the last page. Beginning with next month's issue (August), this listing will show cases reported during the **previous** month, rather than the current month of issue. This change will enable each month's issue of the **Bulletin** to be printed before the end of the month.

Association for Practitioners in Infection Control

Educational Conference in Virginia

1985 APIC-Va. Sponsored Educational Conference

Date: September 26 and 27, 1985

Place: Holiday Inn Fair Oaks, Fairfax, Virginia

Theme: Skill's for the '80's

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